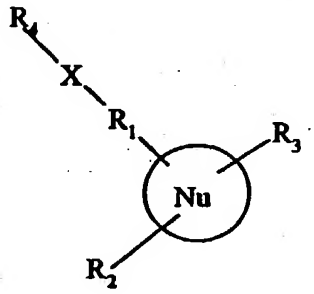
THIAZOLE AND IMIDAZO[4,5-B]PYRIDINE COMPOUNDS AND THEIR PHARMACEUTICAL USE

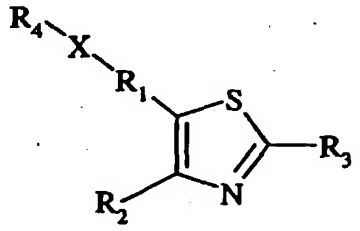
This invention relates to heterocyclic compounds, in particular to thiazoles and imidazopyridines and to their use for treating TNFα and IL-1 mediated diseases such as rheumatoid arthritis and diseases of bone metabolism, e.g. osteoporosis.

Accordingly the present invention provides a compound of formula I

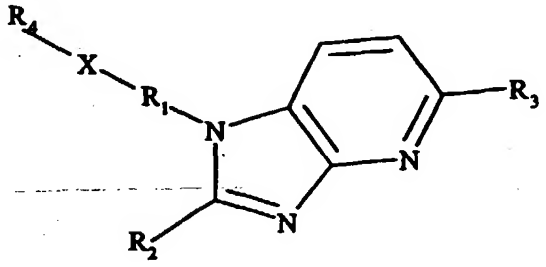


I

wherein Nu is a heterocyclic nucleus selected from a thiazole in which the R_1, R_2 and R_3 substituents are disposed as indicated below



and an imidazo[4,5-b]pyridine in which the R_1, R_2 and R_3 substituents are disposed as indicated below



wherein

R_1 is pyrimidyl or pyridyl;

X is -NR_6-Y-, -O- or -S-,

where R_6 is H, C_1-C_4alkyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_3alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, C_7-C_{19}aralkyl or C_4-C_{19}heteroaralkyl, and -Y- is C_1-C_4alkylene or a direct bond;

R_2 is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF_3,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C_1-C_4alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing an additional hetero atom selected from O, S or N which N is optionally C_1-C_4alkyl C_1-C_4alkylcarbonyl or C_1-C_4alkylthiocarbonyl substitued,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C_1-C_{10}alkoxy, C_2-C_{10}alkenoxy, C_2-C_{10}alkynoxy, C_3-C_7cyclalkoxy, C_5-C_7cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester,

optionally mono- or di-C_1-C_4alkyl-substituted-C_0-C_1alkyl optionally C_1-C_4alkyl- or C_3-C_5 cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C_1-C_4alkoxy, C_2-C_4alkenoxy, C_2-C_4alkynoxy, C_3-C_5cycloalkoxy or C_3-C_5cyclothioalkoxy,

optionally halo substituted C_1-C_4 alkyl,

oxycarbonyl or optionally N-C_1-C_4alkyl-substituted aminocarbonyl both of which are optionally C_1-C_4alkyl or C_3-C_5cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C_1-C_4alkyl-substituted-C_0-C_1alkylamine which is optionally mono-or di-N-C_1-C_4 alkyl substituted,

optionally mono- or di-C_1-C_4alkyl-substituted-C_0-C_1alkyl optionally N-C_1-C_4alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N-C_1-C_4alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C_1-C_4alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_1-C_4alkyl C_1-C_4alkylcarbonyl or C_1-C_4alkylthiocarbonyl substitued, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C_1-C_4alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

optionally mono- or di-C_1-C_4alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_1-C_4alkyl C_1-C_4alkylcarbonyl or C_1-C_4alkylthiocarbonyl substitued;

R_3 is H, amino, C_1-C_{10}alkyl, C_3-C_{10}cycloalkyl, C_3-C_{18}heterocycloalkyl, C_6-C_{18}aryl, or C_3-C_{18}heteroaryl each of which is optionally substituted by up to 4 substituents separately selected from C_1-C_4alkyl, halogen, halo-substitued-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkylthio, C_6-C_{18}aryl, C_3-C_{18} heteroaryl, C_6-C_{18}arylC_1-C_4alkyl, C_3-C_{18} heteroarylC_1-C_4alkyl, C_3-C_{18}heterocycloalkyl or optionally mono- or di-C_1-C_4alkyl substituted amino or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally a further hetero atom selected from O, S or N, all of which are further optionally substituted halo, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy or C_1-C_4alkoxycarbonyl;

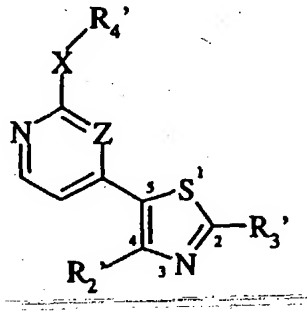
R_4 is C_1-C_{10}alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, or C_3-C_{12}cycloalkyl optionally substituted by up to 3 substituents separately selected from C_1-C_4alkyl, halogen, halo-substitued- C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkylthio, optionally mono- or di-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Above and elsewhere in the present description the terms halo or halogen denote I, Br, Cl or F.

Above and elsewhere in the present description the terms such as "C_3-C_{18}heteroaryl, C_4-C_{19}heteroaralkyl and C_3-C_{18}heterocycloalkyl" denote heteroaryl, heteroaralkyl or heterocycloalkyl substituents comprising at least 3 ring atoms, at least one of which is a hetero atom, e.g.N, O or S, and which in the case of C_4-C_{19}heteroaralkyl groups are attached via an alkylene moiety comprising at least 1 carbon atom.

In particular embodiments the invention provides a compound of formula II



II

wherein

Z is N or CH;

X is $-NR_6-Y-$, -O- or -S-,

where R_6 is H, C_1-C_4alkyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_3alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, C_7-C_{19}aralkyl or C_4-C_{19}heteroaralkyl, and -Y- is C_1-C_4alkylene or a direct bond ;

R_2' is phenyl, optionally substituted by one or more substituents, each of which is independently selected from halo, CF_3, cyano, amido or thioamido, carboxylate or thiocarboxylate, C_1-C_4alkoxy, C_1-C_4alkyl, or NH_2 which is optionally mono-or di-C_1-C_4 alkyl substituted;

R_3' is H, C_1-C_{10}alkyl, C_3-C_{10}cycloalkyl, C_3-C_{18}heterocycloalkyl, C_6-C_{18}aryl, or C_3-C_{18}heteroaryl each of which is optionally substituted by up to 4 substituents separately selected from C_1-C_4alkyl, halogen, halo-substitued-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkylthio, or optionally mono-or di-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_4' is C_6-C_{18}aryl, C_3-C_{18}heteroaryl, or C_3-C_{12}cycloalkyl each of which is optionally substituted by up to 4 substituents separately selected from C_{1-4}alkyl, halogen, halo-substitued-C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, C_{1-4}alkylthio, or optionally mono-or di-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof .

When R_3' is aryl, it is preferably heteroaryl, e.g. pyridyl (e.g. 4-pyridyl) or pyrazyl, each optionally substituted, e.g. by 2 substituents, separately selected from C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, or optionally mono-or di-C_1-C_4alkyl substituted amino.

When R_3' is cycloalkyl it is preferably C_3-C_8, especially C_5-C_6cycloalkyl (e.g. cyclohexyl), optionally substituted, e.g. by 1 or 2 substituents, separately selected from C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, or optionally mono-or di-C_1-C_4alkyl substituted amino.

When R_3' is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom, e.g. N or O, and is optionally substituted, e.g. by 1 or 2 substituents, separately selected from C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, or optionally mono-or di-C_1-C_4alkyl substituted amino.

When R_4' is aryl it is preferably phenyl. When R'_4 is cycloalkyl, it is preferably C_3-C_7 cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. R'_4 may be unsubstituted or substituted, conveniently mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen, C_1-C_4alkyl, halo-substitutedC_1-C_4alkyl, C_1-C_4alkoxy, hydroxy or optionally mono- or di-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N.

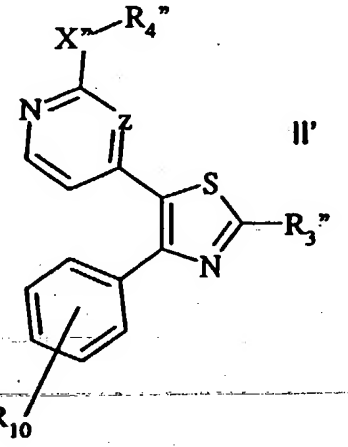
When Y is C_1-C_4 alkylene, it is preferably C_1-C_2 alkylene, and is optionally substituted, e.g. by C_1-C_4alkyl (e.g. methyl), halogen, hydroxy, C_1-C_4alkoxy, or amino.

More preferably R'$_2$ is phenyl substituted, preferably mono- or di-substituted, by halogen or a halogen-containing group, e.g. 4-fluorophen-1-yl, or 3-CF_3, 3-Cl, or 3,4-difluoro substituted phenyl.

More preferably R'$_3$ is H, C_1-C_6alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono- or di-C_{1-4}alkyl substituted amino, each of which is optionally substituted, e.g. by up to 2 substituents, separately selected from C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, or optionally mono-or di-C_1-C_4alkyl substituted amino.

Preferably X is -NH-Y'-, -O- or -S-, where Y' is -CH_2-, -CH_2-CH_2-, -$CH(CH_3)$- or a direct bond

Thus in preferred embodiments the invention provides a compound of formula II'



II'

wherein

R_4'' is phenyl or C_3-C_7cycloalkyl each of which is optionally mono-substituted by halogen, C_1-C_4alkyl, C_1-C_4alkoxy, hydroxy, trihalomethyl or optionally mono-or di-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_{10} is halogen, cyano, amido, thioamid , amino or C_1-C_4alkyl;

R_3'' is H, C_1-C_4alkyl, phenyl, pyridyl, morpholinyl, piperidyl, piperazyl, or optionally mono- or di-C_{1-4}alkyl substituted amino, each of which is optionally substituted, e.g. by up

to 2 substituents, separately selected from C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, or optionally mono-or di-C_1-C_4alkyl substituted amino;

Z is N or CH and

X'' is -NH-Y'-, -O- or -S-, where Y' is $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$ or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Preferably R_4'' is unsubstituted or monosubstituted by halogen, C_1-C_4alkyl (e.g. methyl), C_1-C_4alkoxy (e.g. methoxy), hydroxy or CF_3.

Preferably R_{10} is halogen, e.g. F.

Preferably X'' is -NH-Y' where Y' is $-CH(CH_3)-$.

The Invention includes the following compounds:

4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-methyl-piperidine-1-yl)thiazole;

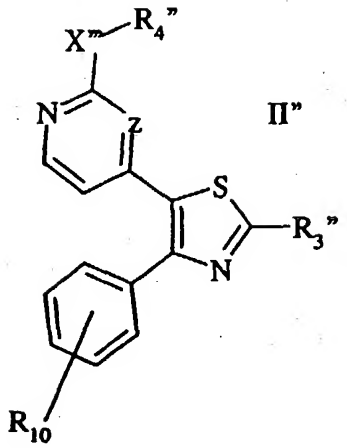
4-(4-Fluorophenyl)-5-(2-[1-(S)-phenylethyl]amino-4-pyrimidinyl)-2-(4-NH-piperidine-1-yl)thiazole;

4-(4-Fluorophenyl)-2-(4-methylpiperidine-1-yl)-5-(2-[cyclopropyl-methyl]amino-4-pyridinyl)thiazole and

4-(4-Fluorophenyl)-2-(4-NH-piperidine-1-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole;

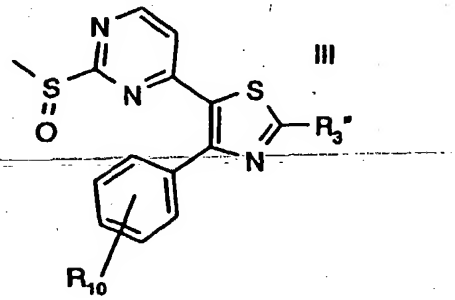
The novel thiazoles of the invention, in particular the compounds of formulae II and II' and the specific compounds listed above are hereinafter referred to "Agents of the Invention".

Agents of the Invention of formula II''

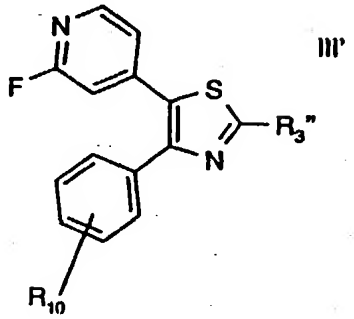


II"

wherein R_3'', R_5'', R_{10} and Z are as previously defined and X''' is -NH-, may be prepared by reacting the corresponding precursor compound of formula III or III'



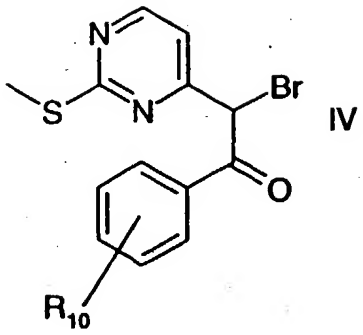
III



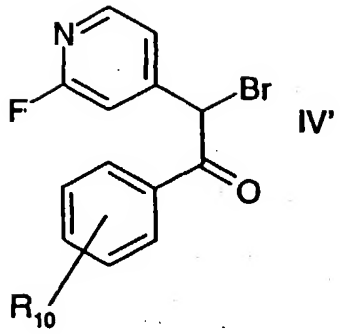
III'

wherein R_3'' and R_{10} are as previously defined, with the corresponding R_4''-NH_2 derivative. For example, the reaction may be carried out by refluxing the reactants in an organic solvent, e.g. dichloroethane, e.g. in the presence of diethoxytrifluoroborane. Thereafter, if desired, the compound of Formula II" obtained may be converted into a further compound of Formula II" or otherwise treated as required.

The precursor compound of formula III may be prepared by controlled oxidation of the corresponding 5(2-methylthio-4-pyrimidinyl)-4-phenythiazole, e.g. employing an oxidising agent such as mCPBA (meta chloroperbenzoic acid), conveniently in an organic solvent such as methylene chloride. The corresponding 5(-4-pyrimidinyl/pyridinyl)-4-phenylthiazole compound may be prepared by contacting th corresponding acetophenone precursor compound of formula IV or IV'



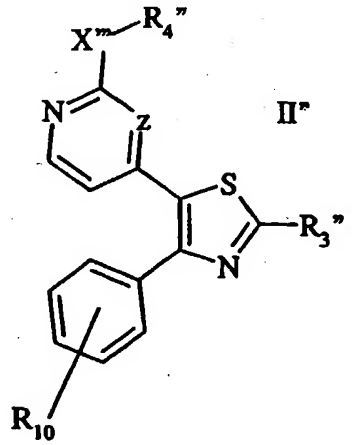
IV



IV'

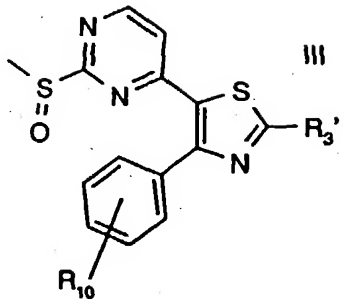
wherein R_{10} is as defined above, with a corresponding thioamide of formula R_3'C(S)NH_2, typically at elevated temperature. The compounds of formula IV and IV' may be prepared by bromination of the corresponding acetophenone, e.g. 2-(2-methylthio-4-pyrimidinyl)acetophenone. The acetophenone precursor may be prepared by reacting the corresponding N-methoxy-N-methylbenzamide with the corresponding pyrimidine, e.g. 4-methyl-2-(methylthio) pyrimidine, for instance in a THF containing organic solvent with cooling.

Thus in a further aspect the invention includes a process for the preparation of a compound of formula II''

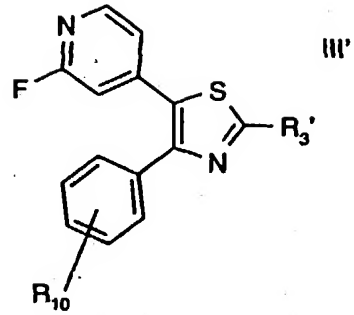


II''

wherein R_3'', R_4'', R_{10} and Z are as previously defined and X''' is -NH-, which comprises reacting the corresponding precursor compound of formula III or III'



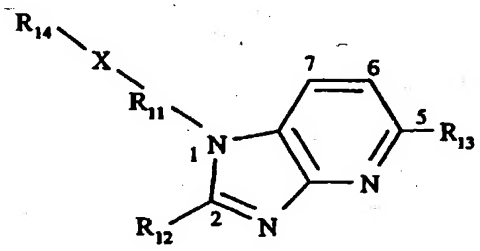
III



III'

wherein R_3'' and R_{10} are as previously defined, with the corresponding R_4''-NH_2 amine, and thereafter, if desired, converting the compound of formula II" obtained into a further compound of formula II" or a pharmaceutically-acceptable and -cleavable ester thereof or acid addition salt thereof.

In further particular embodiments the invention provides a compound of formula V



V

wherein

R_{11} is pyrimidyl;

X is -NR_6-Y-, -O- or -S-,

where R_6 is H, C_1-C_4alkyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_3alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, C_7-C_{19}aralkyl or C_4-C_{19}heteroaralkyl, and -Y- is C_{1-4}alkylene or a direct bond ;

R_{12} is phenyl, optionally substituted by one or more substituents, each of which is independently selected from

halo,

CF_3,

cyano,

amido or thioamido which is optionally mono- or di-N-substituted by C_1-C_4alkyl or the N atom of which forms a 5-7 membered heterocyclic ring optionally containing

an additional hetero atom selected from O, S or N which N is optionally C_1-C_4alkyl C_1-C_4alkylcarbonyl or C_1-C_4alkylthiocarbonyl substitued,

carboxylate or thiocarboxylate optionally in the form of an optionally halo-substituted C_1-C_{10}alkoxy, C_2-C_{10}alkenoxy, C_2-C_{10}alkynoxy, C_3-C_7cyclalkoxy, C_5-C_7cycloalkenoxy, aryloxy, arylalkoxy, heteroaryloxy or heteroarylalkoxy ester,

optionally mono- or di-C_1-C_4alkyl-substituted-C_0-C_1alkyl optionally C_1-C_4alkyl- or C_3-C_5 cycloalkyl-substituted-carbonyl or -thiocarbonyl,

optionally halo-substituted-C_1-C_4alkoxy, C_2-C_4alkenoxy, C_2-C_4alkynoxy, C_3-C_5cycloalkoxy or C_3-C_5cyclothioalkoxy,

optionally halo substituted C_1-C_4 alkyl,

oxycarbonyl or optionally N-C_1-C_4alkyl-substituted aminocarbonyl both of which are optionally C_1-C_4alkyl or C_3-C_5cycloalkyl substituted (including thiocarbonyl analogues thereof),

optionally mono- or di-C_1-C_4alkyl-substituted-C_0-C_1alkylamine which is optionally mono-or di-N-C_1-C_4 alkyl substituted,

optionally mono- or di-C_1-C_4alkyl-substituted-C_0-C_1alkyl optionally N-C_1-C_4alkyl-substituted amino-carbonyl or -thiocarbonyl,

optionally N-C_1-C_4alkyl-substituted amino-sulphinyl or -sulphonyl optionally substituted by

optionally mono- or di-N-C_1-C_4alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_1-C_4alkyl C_1-C_4alkylcarbonyl or C_1-C_4alkylthiocarbonyl substituted, or

sulphinyl or sulphonyl optionally substituted by

optionally halo-substituted-C_1-C_4alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

optionally mono- or di-N-C_1-C_4alkyl-substituted amino,

a nitrogen atom which form a heterocyclic ring of 5 to 7 members optionally containing an additional heteroatom selected from O, S or N which N is optionally C_1-C_4alkyl C_1-C_4alkylcarbonyl or C_1-C_4alkylthiocarbonyl substituted;

R_{13} is H, amino, C_1-C_{10}alkyl, C_3-C_{10}cycloalkyl, C_3-C_{18}heterocycloalkyl, C_6-C_{18}aryl, or C_3-C_{18}heteroaryl all optionally substituted by up to 4 substituents separately selected from C_1-C_4alkyl, halogen, halo-substitued-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkylthio, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, C_6-C_{18}arylC_1-C_4alkyl, C_3-C_{18}heteroarylC_1-C_4alkyl, C_3-C_{18}heterocycloalkyl or optionally mono- or di-N-C_1-C_4alkyl substituted amino all of which are optionally substituted by halo, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy or C_1-C_4alkoxycarbonyl;

R_{14} is C_1-C_{10}alkyl, C_6-C_{18}aryl, C_3-C_{18}heteroaryl, or C_3-C_{12}cycloalkyl optionally substituted by up to 3 substituents separately selected from C_1-C_4alkyl, halogen, halo-substitued-C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, C_1-C_4alkylthio, optionally mono- or di-N-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N,

and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof .

R_{11} is preferably 4-pyrimidyl.

When R_{13} is alkyl it is C_1-C_{10}alkyl, preferably C_1-C_6alkyl, optionally substituted, preferably with one or two substituents separately selected from hydroxy, C_1-C_4alkoxy, amino optionally mono-or disubstituted by C_1-C_4alkyl or N-heterocyclyl containing from 5 to 7 ring and optionally containing a further hetero atom (e.g. O, S or N).

When R_{13} is aryl or heteroaryl either of which is optionally substituted by up to 4 substituents, R_{13} may comprise one of the customary aryl or heteroaryl substituents in the art and may be substituted as is customary in the art; for instance as defined for the substituent R_3 of WO 93/03297. For instance, R_{13} may comprise a phenyl, pyridyl or pyrimidyl, substituent optionally substituted by up to 5 substituents separately selected from C_1-C_4alkyl, halogen, halo-substituted C_1-C_4alkyl, hydroxy, C_1-C_4alkoxy, or optionally mono- or di-C_1-C_4alkyl substituted amino.

When R_{13} is substituted amino it may be substituted by one or two substitutents independently selected from C_1-C_4alkyl, C_6-C_{18}aryl, C_3-C_{18} heteroaryl, C_6-C_{18}arylC_1-C_4alkyl, C_3-

C_{18} heteroarylC_1-C_4alkyl, all of which are optionally substituted by halo, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy or C_1-C_4alkoxycarbonyl.

When R_{13} is cycloalkyl it is preferably C_3-C_8, especially C_5-C_6cycloalkyl (e.g. cyclohexyl), optionally substituted, preferably with up to 2 substituents separately selected from C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy, or optionally mono- or di-C_1-C_4alkyl substituted amino.

When R_{13} is heterocycloalkyl it is preferably N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N, optionally substituted, e.g. by up to 2 substituents, selected from halogen, hydroxy, alkoxy, or optionally mono- or di-C_1-C_4alkyl substituted amino. For instance, R_{13} may be an optionally substituted morpholino, piperazyl or piperidyl substituent.

When R_{14} is aryl it is preferably phenyl. When R_{14} is cycloalkyl, it is preferably C_3-C_7 cycloalkyl, e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl. R_{14} may be unsubstituted or substituted, conveniently mono-substituted, e.g. phenyl conveniently meta or para substituted, by halogen, C_1-C_4alkyl, halo-substitued C_1-C_4alkyl, C_1-C_4alkoxy, hydroxy, optionally mono- or di-N-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N.

When -Y- is C_1-C_4 alkylene, it is preferably C_1-C_2 alkylene, and is optionally substituted, e.g. by C_1-C_4alkyl (e.g. methyl), halogen, hydroxy, C_1-C_4alkoxy, or amino.

Preferably R_{12} is phenyl substituted with 1-3 substituents, preferably mono-substituted, selected from halogen, CN, halo-substituted alkyl, e.g. CF_3, C_1-C_4alkyl, or C_1-C_4alkoxy. Most preferably R_2 is phenyl mono-substituted by halogen, e.g. 4-flurophenyl.

In particular embodiments R_{13} is pyridyl, pyrimidyl, piperazyl, piperidyl, $-NR_9R_{10}$, $-CH_2OH$, $-CH_2NR_{15}R_{16}$, $-CH_2CH_2R_{15}R_{16}$, or Het-C_{1-4}alkyl-,

wherein

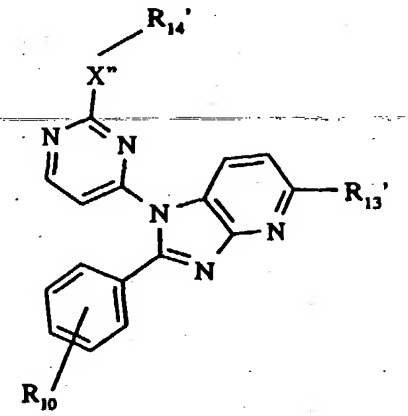
R_9 and R_{10} are separately selected from H, C_1-C_4alkyl, C_6-C_{18}aryl, C_3-C_{18} heteroaryl, C_6-C_{18}arylC_1-C_4alkyl, C_3-C_{18}heteroarylC_1-C_4alkyl all of which are optionally substituted by halo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkoxycarbonyl,

R_{15} and R_{16} are separately selected from H or C_1-C_4alkyl, and

Het is N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O, S or N).

Preferably X is -NH-Y'-, -O- or -S-, where Y' is $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$ or a direct bond. Most preferably X is NH-Y"-, where Y" is $-CH(CH_3)-$ or a direct bond.

Thus in preferred embodiments the invention provides a compound of formula V'



V'

wherein

R_{14}' is phenyl or C_3-C_7cycloalkyl each of which is optionally mono-substituted by halogen, C_1-C_4alkyl, C_1-C_4alkoxy, hydroxy, trihalomethyl optionally mono- or di-N-C_1-C_4alkyl substituted amino, or by N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom selected from O, S or N;

R_{10} is halogen, CF_3, C_1-C_4alkyl or C_1-C_4alkoxy;

R_{13}' is pyridyl, pyrimidyl, piperazinyl, piperidinyl, NR_9R_{10}, $-CH_2OH$, $CH_2NR_{15}R_{16}$, $-CH_2CH_2R_{15}R_{16}$, or Het-C_1-C_4alkyl-,

wherein

R_9 and R_{10} are separately selected from H, C_1-C_4alkyl, C_6-C_{18}aryl, C_3-C_{18} heteroaryl, C_6-C_{18}arylC_1-C_4alkyl, C_3-C_{18}heteroarylC_1-C_4alkyl all of which are optionally substituted by halo, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkoxycarbonyl,

R_{11} and R_{12} are separately selected from H or C_1-C_6alkyl, and

Het is N-heterocyclyl containing from 5 to 7 ring atoms and optionally containing a further hetero atom (e.g. O,S or N)

X'' is -NH-Y'-, -O- or -S-, where Y' is $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$ or a direct bond, and pharmaceutically-acceptable and -cleavable esters thereof and acid addition salts thereof.

Preferably R_{14}' is phenyl or cyclopentyl, cyclobutyl or cyclopropyl.

Preferably R_{10} is halogen.

Preferably X'' is -NH-Y'' where Y'' is $-CH(CH_3)-$ or a direct bond.

The Invention includes the following compounds:

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(N,N-diethylamino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(isopropylamino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyrrolidino-N-2-ethyl)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-pyridyl)imidazo[4,5-b] pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridyl)imidazo[4,5-b] pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl) imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino -4-pyrimidinyl)-5-(4-methyl-1-piperazinyl) imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-piperidinyl) imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-methyl-4-piperidinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyl)imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(benzylamino) imidazo[4,5-b]pyridine;
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino) imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-fluorophenyl amino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyridyl-4-amino)imidazo[4,5-b]pyridine;

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonyl piperidine-4-amino)imidazo[4,5-b]pyridine, and

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidine-4-amino)imidazo[4,5-b]pyridine.

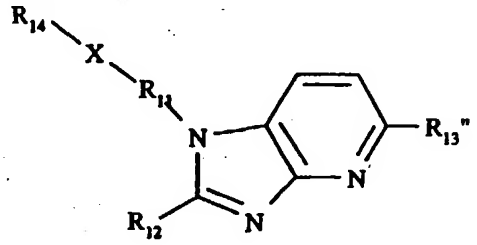
The novel imidazopyridines of the invention, in particular the compounds of formulae V and V' and the specific compounds listed above are hereinafter also referred to as "Agents of the Invention".

It will be appreciated that certain Agents of the Invention may contain at least 1 assymetric carbon atom; for instance when Y is substituted alkylene, e.g. when Y" is -CH(CH_3)- for the compounds of formula II' or V' above. The resulting diastereomers and enantiomers are encompassed by the instant invention. Preferably, however, e.g. for pharmaceutical use in accordance with the invention, the compounds of formula I, are provided in pure or substantially pure epimeric form, e.g. as compositions in which the compounds are present in a form comprising at least 90%, e.g. preferably at least 95% of a single epimer (i.e. comprising less than 10%, e.g. preferably less than 5% of other epimeric forms). Preferred epimeric compounds of formula I are described hereinafter in the Examples.

The Agents of the Invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

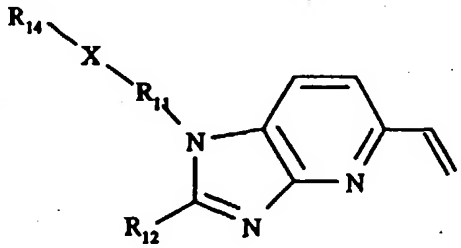
Agents of the Invention may also exist in the form of pharmaceutically acceptable salts, and as such are included within the scope of the invention. Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example, mineral acids, e.g., hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

Agents of the Invention of Formula V"



V"

wherein R_{11}, R_{12}, R_{14} and X are as previously defined and R_{13}" is $-CH_2-CH_2NR_{15}R_{16}$ or $-CH_2-CH_2$-Het wherein R_{15}, R_{16} and Het are as defined above may be prepared by reacting a corresponding vinyl precursor compound of formula VI

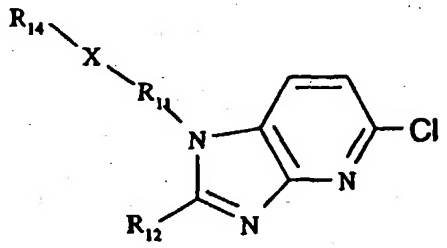


VI

wherein R_{11}, R_{12}, R_{14} and X are as previously defined, with the corresponding amine of formula $HNR_{15}R_{16}$ or N-heterocycloalkyl ring compound. For instance the reaction may be carried out by

refluxing the reactants, e.g. in acetic acid, followed by treatment with a mild base, e.g. Na_2CO_3.

The precursor compound of formula VI may be prepared by reacting the corresponding 5-chloro-imidazopyridine of formula VII



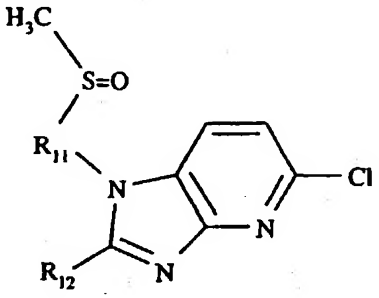
VII

wherein R_{11}, R_{12}, R_{14} and X as are as previously defined, with a vinylating agent. For instance the chloro compound of formula VII is reacted with vinyltributylstannane in the presence of $PdCl_2(PPh_3)_2$ in xylene at elevated temperature, e.g. 160°C, under an inert atmosphere.

Agents of the Invention of formula V, wherein R_{13} is aryl or heteroaryl may be prepared from chloroprecursor compounds of formula VII, as defined above, by arylation or heteroarylation. For instance the compound of formula VII is heated with the corresponding trialkylstannyl-aryl or -heteroaryl, e.g. tributylstannylaryl- or trimethylstannyl-aryl or -heteroaryl, compound e.g. to about 150°C under an inert atmosphere.

Agents of the Invention of formula V, wherein R_{13} is -N-heterocycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -NH-(C_1- C_4alkyl)-heterocycloalkyl, -NH-(C_1- C_4alkyl)-aryl, -NH-(C_1- C_4alkyl)-heteroaryl, or -NH-(C_1- C_4alkyl)-heterocycloalkyl may be prepared from chloroprecursor compounds of formula VII, as defined above, by coupling with the corresponding N-heterocycloalkyl compound or amine. The coupling reaction may carried out using Buchwald chemisty. For instance, to a solution of the chloroprecursor compound of formula VII and a suitable ligand, e.g. BINAP, in an inert organic solvent such as xylene is added the N-heterocycloalkyl compound or amine together with an organic base, e.g. sodium tertiary butylate, and the reaction mixture heated, e.g. to 160°C for 10 minutes under argon; after which the product may be recovered by pouring the reaction mixture onto water and solvent extraction, e.g. with TBME.

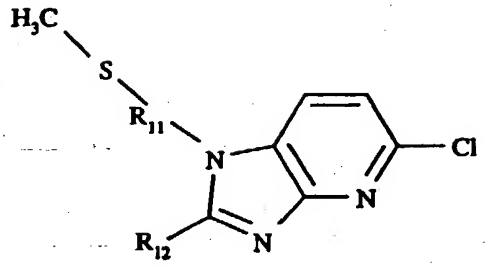
The compounds of formula VII in which X is -NH- may be prepared by reacting the corresponding methylsulphinyl compound of formula VIII



VIII

wherein R_{11} and R_{12} are as previously defined, with the corresponding amine of formula R_{14}-NH_2. For instance, the reactants are mixed and heated, e.g. to 80°C for 1h.

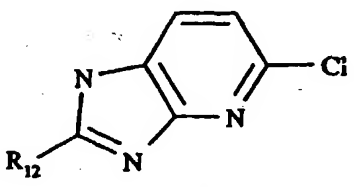
The methylsulphinyl compound of formula VIII prepared by oxidation of the corresponding methylthio compound of formula IX.



IX

wherein R_{11} and R_{12} are as previously defined; for instance, by treating the compound of formula IX in solution, e.g. CH_2Cl_2/HOAc solution, with mCPBA, e.g. at 0°C for 30 min., followed by treatment with mild base, e.g. Na_2CO_3.

The methylthio compound of formula IX may be prepared by coupling the corresponding 1-H-imidazopyridine compound of formula X

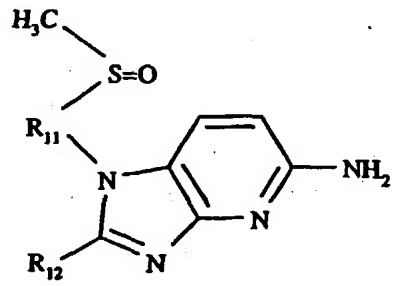


X

wherein R_{12} is as defined above, with 2-methylthio-4-iodopyrimidine. For instance, $KN(TMS)_2$ solution, e.g. in toluene, is added at 0°C to a solution of X, e.g. in DMF with mixing, and 2-methyl-4-iodopyrimidine solution e.g. in toluene, is added and the reaction mixture heated e.g. at 120°C for 20h.

The compound of formula X may be prepared by coupling 2,3-diamino-6-chloropyridine with the corresponding acid of formula $R_{12}COOH$; for instance, by treating a mixture of the reactants with polyphosphonic acid e.g. at 150°C for 6h, followed by neutralisation e.g. with cold concentrated aqueous NH_3.

Compounds of formula V in which R_{13} is NH_2 may be prepared by reacting the corresponding methyl sulphinyl compound of formula VIII'



VIII'

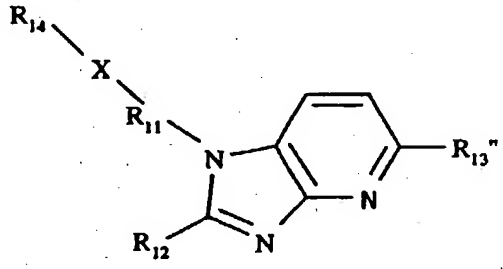
wherein R_{11} and R_{12} are as previously defined, with the corresponding amine of formula R_{14}-NH_2, for instance, as described above for the compound of formula VI. The compound of formula VIII' and precursors therefor may be prepared by analogy with the compound of formula VIII and the precursors thereof; for instance, as described above.

Agents of the Invention which are 5-(4-NH-1-piperazyl)imidazopyridines of formula V in which R_{13} is piperazyl and precursors therefor may be prepared by analogy to the pr paration of the compound of formula VIII' and the precursors thereof. Conveniently the free nitrogen atom of the piperazine ring is protected e.g. with a tert. butoxycarbonyl residue, during precursor preparation as appropriate. 5-(4-NH-1-piperazyl)imidazopyridines of formula I may be converted

to 5-(4-substituted piperazyl)imidazopyridine Agents of the Invention as desired; for instance, as hereinafter described in the Examples.

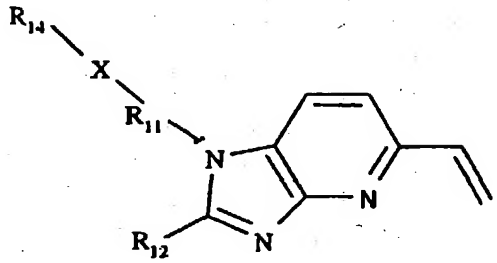
Accordingly in a further aspect the invention provides a process for the production of

(i) an Agent of the Invention of formula V"



V"

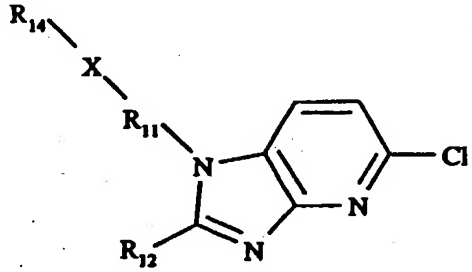
wherein R_{11}, R_{12}, R_{14} and X are as previously defined and R_{13}" is $-CH_2-CH_2NR_{15}R_{16}$ or $-CH_2-CH_2$-Het wherein R_{15}, R_{16} and Het are as previously defined comprising reacting a corresponding vinyl precursor of formula VI



VI

wherein R_{11}, R_{12}, R_{14} and X are as previously defined with the corresponding amine of formula $HNR_{15}R_{16}$ or N-heterocycloalkyl ring compound;

(ii) an Agent of the Invention of formula V wherein R_{13} is aryl or heteroaryl comprising arylation or heteroarylation of a compound of formula VII

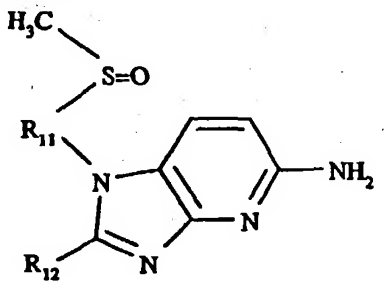


VII

wherein R_{11}, R_{12}, R_{14} and X are as previously defined;

(iii) an Agent of the Invention of formula V wherein R_{13} is -N-heterocycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -NH-(C_1- C_4alkyl)-heterocycloalkyl, -NH-(C_1- C_4alkyl)-aryl, -NH-(C_1- C_4alkyl)-heteroaryl, or -NH-(C_1- C_4alkyl)-heterocycloalkyl comprising coupling a corresponding chloroprecursor compound of formula VII, as defined above, with the corresponding N-heterocycloalkyl compound or amine;

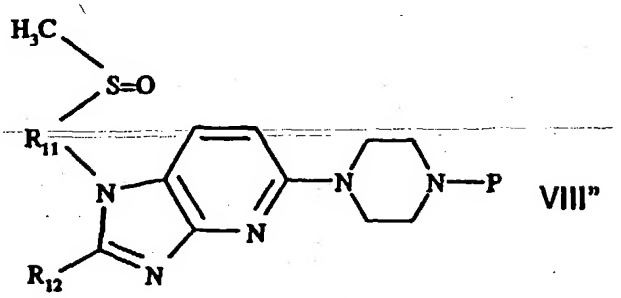
(iv) an Agent of the Invention of formula V in which R_{13} is $-NH_2$, comprising reacting the corresponding methyl sulphinyl compound of formula VIII'



VIII'

wherein R_{11}, and R_{12} are as previously defined, with the corresponding amine of formula R_{14}-NH_2, and

(v) an Agent of the Invention of formula V in which R_{13} is piperazinyl, comprising reacting a corresponding methylsulphinyl compound of formula VIII"



VIII"

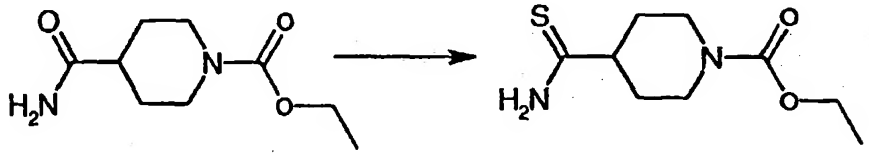
wherein R_{11} and R_{12} are as previously defined and P is an N protecting group, with the corresponding amine of formula R_{14}-NH_2.

The synthesis of Agents of the Invention is further described in the following Examples.

EXAMPLES

Example 1 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole

a) N-Ethoxycarbonylpiperidine-4-thiocarboxamide

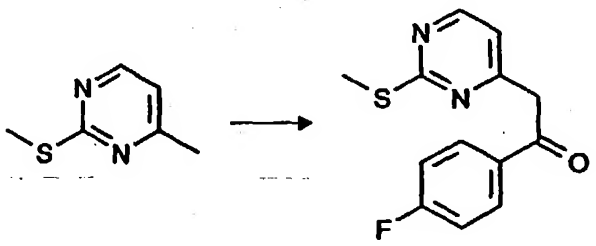


N-Ethoxycarbonylpiperidine-4-carboxamide (6g 30mmol) in toluene (300ml) is treated with Lawesson's reagent (6.1g 15mmol) at room teperature for 18h. The reaction mixture is evaporated and purified by SiO_2 chromatography (acetone/cyclohexane 20/80) to yield the title compound, which is recrystallised from hexanes (3.6g 52.5%)

1H-NMR (400MHz; $CDCl_3$): 1.28 (t, 3H); 1.72-1.83 (dq, 2H); 1.95 (d, 2H); 2.68-2.88 (m, 3H); 4.18 (q, 2H); 4.30 (bs, 2H); 6.92 (bs, 1H, NH); 7.51 (bs, 1H, NH)

MS (m/z) CI: 217 (MH+, 50); 171 (100).

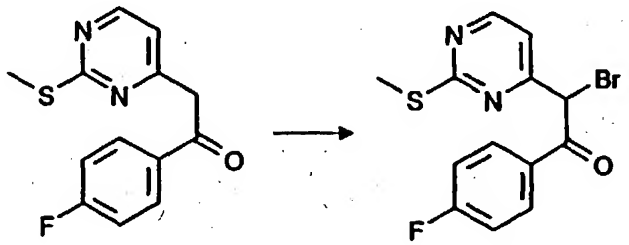
b) 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone



n-BuLi (10 ml of a 1.6 M solution in hexane; 12 mmol) is added at -78°C to a solution of diisopropylamine (2.48 ml; 17 mmol) in THF (15 ml) and stirred for 5 min. 4-Methyl-2-(methylthio)pyrimidine (2g; 14.5 mmol) dissolved in THF (2 ml) is added dropwise and stirred for 30 min at -78 C. 4-Fluoro-N-methoxy-N-methylbenzamide (2.66 g; 14.5 mmol) is dissolved in THF (3 ml) and added slowly to the reaction mixture. The mixture is warmed to r.t. within 45 min. and poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.5 g (65%) of yellow crystals after recrystallisation from tert.butyl methyl ether/hexane.

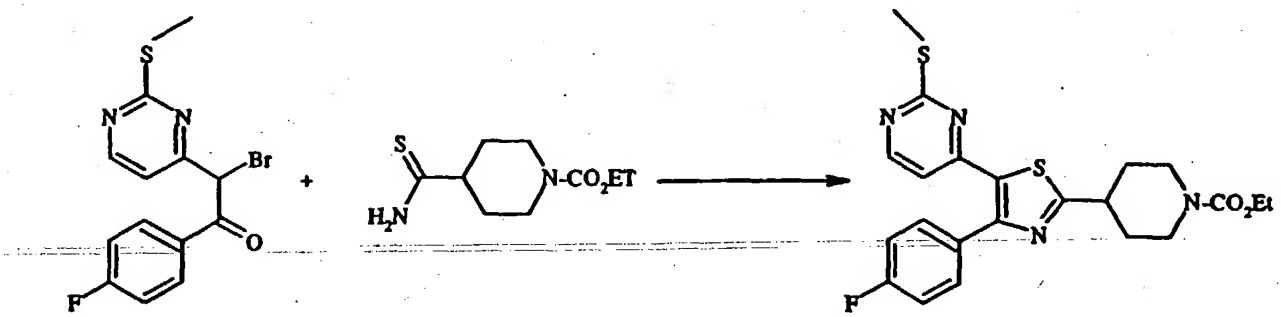
1H-NMR (200 MHz $CDCl_3$): 3.00 (s, 3H); 6.30 (s, 1H; vinyl-H of enol); 7.00 (d, 1H); 7.50 (dd, 2H); 8.20 (dd, 2H); 8.7 (d, 2H). Due to pH-dependent keto-enol tautomery, signals may be duplicated.

c) 4-Fluoro-2-bromo -2-(2-methylthio-4-pyrimidinyl)acetophenone



Bromine (1.22g; 7.6 mmol) in acetic acid (5.6 ml) is added to a solution of 4-Fluoro-2-(2-methylthio-4-pyrimidinyl)acetophenone (2g; 7.6 mmol) in acetic acid (40 ml). The initially thick precipitate is almost dissolved after 20 min., filtered and the filtrate evaporated to dryness. The residue is taken up in a saturated solution of $NaHCO_3$ and extracted three times with tert.butyl methyl ether. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield 2.6 g (100%) of a brown oil, which is used in the next step without purification.

d) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylthio-4-pyrimidinyl)thiazole



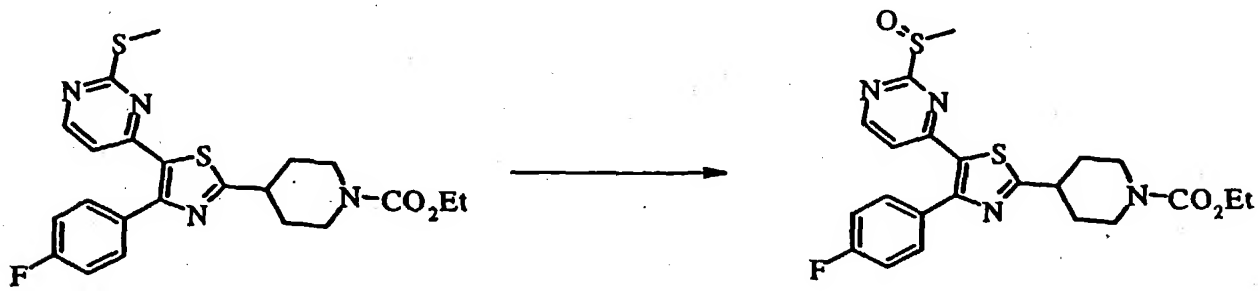
Na_2SO_4 (6.9g 40mmol) in DMF (100ml) is heated at 120°C for 10min. N-Ethoxycarbonyl-piperidine-4-thiocarboxamide (8.6g 40mmol) is added as a solid and heating continued for 5min.

2-Bromo-2-(2-methylthio-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone (6.8g 20mmol) in DMF (20ml) is rapidly added within 3 seconds and stirring continued at 120°C for 10min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (ethyl acetate/hexanes 5/95 to 10/90) to yield the title compound as yellow crystals (2.2g 24%)

1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.78-1.92 (dq, 2H); 2.21 (bd, 2H); 2.58 (s, 3H); 2.91-3.03 (bt, 2H); 3.18-3.28 (m, 1H); 4.20 (q, 2H); 4.25-4.40 (bs, 2H); 6.75 (d, 1H); 7.15 (t, 2H); 7.57 (dd, 2H); 8.31 (d, 1H).

MS (m/z) ESI: 459 (MH+,100).

e) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylsulfinyl-4-pyrimidinyl)thiazole

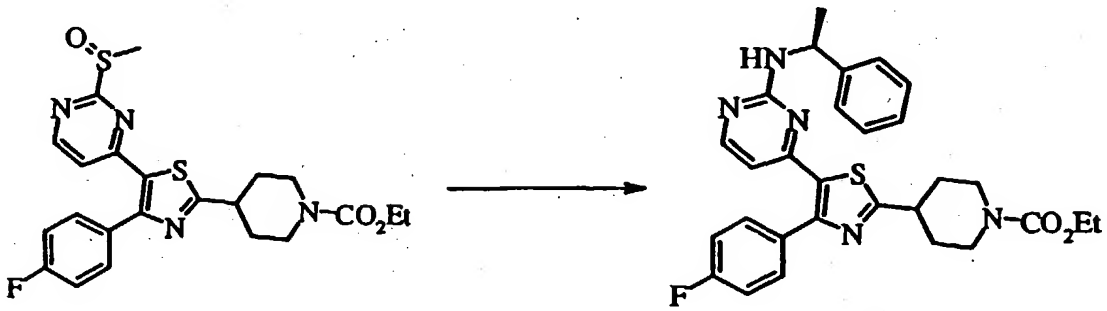


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylthio-4-pyrimidinyl)thiazole (4.0g 8.7mmol) in CH2Cl2 (80ml) is treated with mCPBA (70% 2.1g 8.7mmol) at 0°C for 15min. The reaction mixture is poured on 2N Na_2CO_3 and extracted with CH_2Cl_2 three times. The combined organic phases were dried over Na2SO4, filtered, evaporated to dryness and purified by SiO_2 chromatography (acetone/hexanes 20/80 to 50/80) to yield the title compound (2.2g 53%) as a white foam.

1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.78-1.92 (dq, 2H); 2.21 (bd, 2H); 3.00 (s, 3H); 2.90-3.02 (m, 2H); 3.20-3.30 (bt, 1H); 4.18 (q, 2H); 4.25-4.40 (bs, 2H); 7.15 (d, 1H); 7.20 (t, 2H); 7.56 (dd, 2H); 8.63 (d, 1H).

MS (m/z) ESI: 475 (MH+).

f) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole

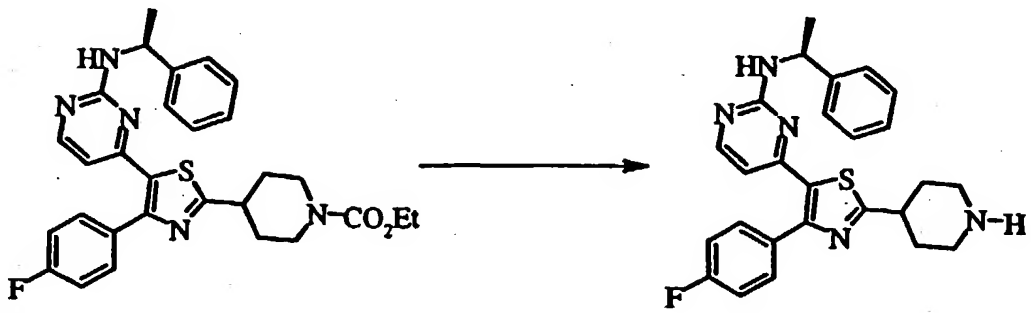


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(methylsulfinyl-4-pyrimidinyl)thiazole (2.2g 4.6mmol) and 1-(S)-phenylethylamine (2.2ml) are heated at 100°C for 1h. Purification over SiO_2 (acetone/cyclohexane 10/90 to 20/80) yielded the title compound as a pale yellow foam (2.4g 95%).

1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.51 (d, 3H); 1.75-1.88 (bq, 2H); 2.18 (bd (2H); 2.97 (bt, 2H); 3.20 (tt, 1H); 4.20 (q, 2H); 4.30 (bs, 2H); 5.17 (m, 1H); 5.46 (d, 1H, NH); 6.35 (d, 1H); 7.12 (t, 2H); 7.30-7.45 (m, 5H); 7.55 (dd, 2H); 8.08 (d, 1H).

MS (m/z) ESI: 523 (MH+, 100).

g) 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole

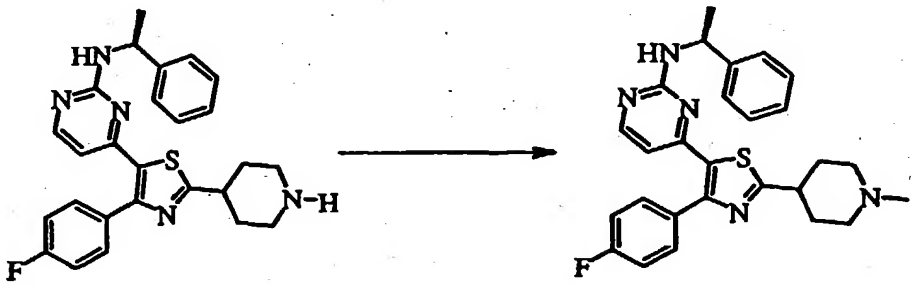


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)thiazole (2.4g 4.5mmol) was dissolved in $CHCl_3$ (45ml) and treated with Me_3SiI (1.8ml 13.5mmol) at 60°C for 6h. The reaction mixture was combined with 6M HCl in propanol (18.5ml), homogenized by vigorous stirring, poured on 2N NaOH and extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether /MeOH/NH3conc. 95/4.5/0.5 to 80/18/2) to yield the title compound (1.8g 87%) as a white foam.

1H-NMR (400MHz; $CDCl_3$): 1.51 (d, 3H); 1.75-1.88 (bq, 2H); 2.18 (bd (2H); 2.82 (dt, 2H); 3.18 (tt, 1H); 3.25 (d, 2H); 5.17 (m, 1H); 5.45 (d, 1H, NH); 6.32 (d, 1H); 7.12 (t, 2H); 7.30-7.47 (m, 5H); 7.56 (dd, 2H); 8.07 (d, 1H).

MS (m/z) ESI: 460 (MH+, 100).

Example 2; 4-(4-Fluorophenyl)-2-(1-methylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole



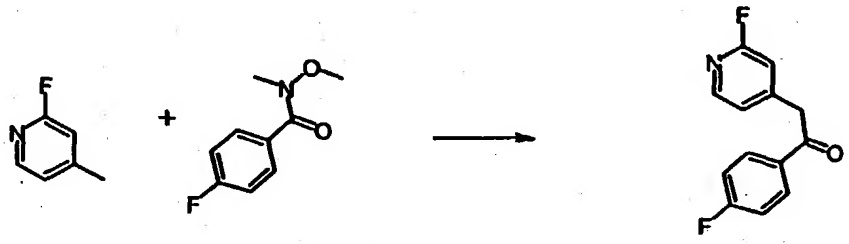
4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl) thiazole (575mg 1.25mmol) is dissolved in MeOH (12ml) and treated with an aqueous 36%-solution of formaldehyde (0.2ml 2.5mmol) and $NaBH_4$ (95mg 2.5mmol), which is added as a solid in 3 portions. After 30min at room temperature the reaction mixture is poured on water and extracted three times with ethyl acetate. The combined organic phases are dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether /MeOH / NH_3conc. 95/4.5/0.5 to 90/9/1) to yield the title compound (600mg 85%) as pale yellow foam.

1H-NMR (400MHz; $CDCl_3$): 1.51 (d, 3H); 1.88-2.01 (m, 2H); 2.08-2.25 (m, 4H); 2.48 (s, 3H); 2.97-3.08 (m, 3H); 5.18 (m, 1H); 5.48 (d, 1H, NH); 6.33 (d, 1H); 7.12 (t, 2H); 7.30-7.47 (m, 5H); 7.56 (dd, 2H); 8.05 (d, 1H).

MS (m/z) ESI: 474 (MH+, 100).

Example 3 4-(4-Fluorophenyl)-2-(piperidin-4-yl).5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

a) 4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone

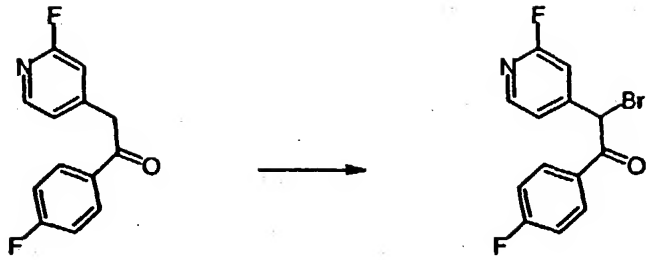


Diisopropylamine (0.93 ml; 6.55 mmol) in THF (6 ml) is cooled to –78 C and treated with nBuLi (3.8 ml; 6.08 mmol of a 1.6 M solution in hexane). 2-Fluoro-4-methylpyridine (620 mg; 5.4 mmol) is added dropwise and stirred under argon for 30 min. 4-Fluoro-N-methoxy-N-methylbenzamide (1 g; 5.46 mmol) is added dropwise in THF (0.5 ml) and the reaction mixture allowed to warm up to room temperature within 10 min. then poured on a saturated solution of NaCl and extracted with TBME three times. The combined organic phases are washed with water, dried over Na_2SO_4, filtered and evaporated to dryness to yield the title compound as pale yellow crystals. Purification by recrystallisation from hot TBME rendered the desired compound as white solid (630 mg; 50 %).

1H-NMR (200 MHz; $CDCl_3$): 4.35 (s, 2H); 6.88 (s, 1H); 7.08-7.30 (m, 3H); 7.99-8.15 (dd, 2H); 8.20 (d, 1H).

MS (e/z) ESI: 233 (M+, 5); 123 (100).

b) 4-Fluoro-2-bromo-(2-fluoropyridin-4-yl)acetophenone

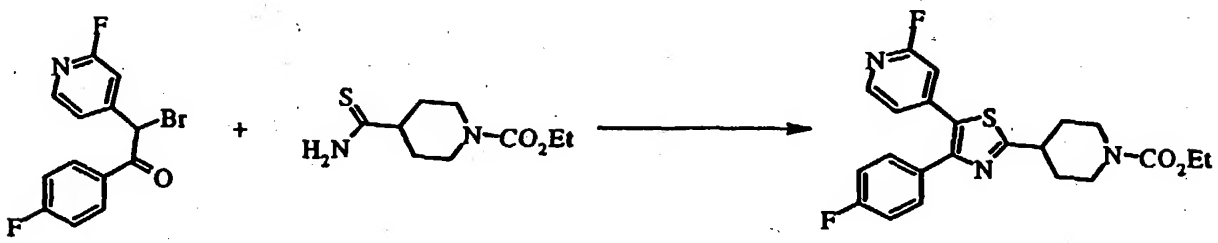


4-Fluoro-2-(2-fluoropyridin-4-yl)acetophenone (0.5 g; 2.1 mmol) dissolved in acetic acid (4 ml) is treated with bromine (0.34 g; 2.1 mmol) in acetic acid (1 ml) at room temperature for 2.5 h under stirring. The light brown solution is evaporated to dryness, dissolved in ether and extracted three times with diethyl ether.The combined organic phases are washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to dryness to yield the title compound as pale yellow oil (0.67 g; 100%).

1H-NMR (200 MHz; $CDCl_3$): 6.15 (s, 1H); 7.10-7.38 (m, 4H); 8.08 (dd, 2H); 8.23 (d, 1H).

MS (e/z) ESI: 232 (M-Br); 204 (10); 203 (12); 123 (100).

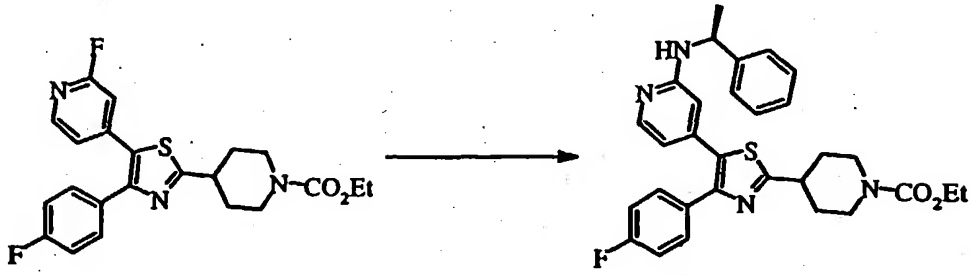
c) 4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-fluoro-4-pyridinyl)thiazole



2-Bromo-2-(2-fluoro-4-pyridyl)-1-(4-fluorophenyl)ethanone (2.5g 8.0mmol) and N-ethoxycarbonyl-piperidine-4-thiocarboxamide (2.1g 9.6mmol) are heated at 60°C in DMF (4ml) for 30min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (ethyl acetate/cyclohexane 20/80 to 100/0) to yield the title compound as an oil (2.5g 70%)

MS (m/z) ESI: 430 (MH+)

d) 4-(4-Fluorophenyl)-2-(1-eth xycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole

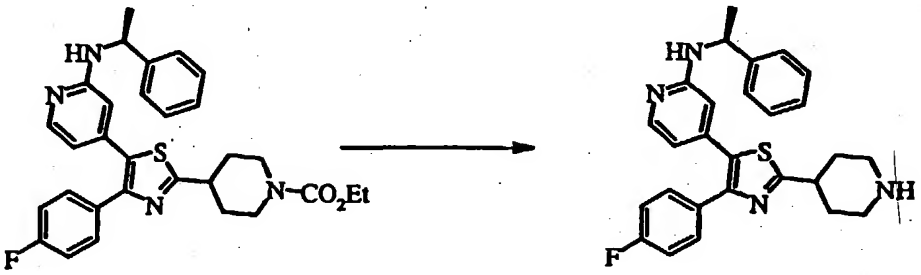


4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-fluoro-4-pyridinyl)thiazole (2.4g 5.5mmol) and 1-(S)-phenylethylamine (5.5ml) are heated to 195°C for 5h. The reaction mixture is evaporated and purified by SiO_2 chromatography (ethyl acetate/cyclohexane 20/80 to 30/70) to yield the title compound as a white foam (2.0g 67.3%)

1H-NMR (400MHz; $CDCl_3$): 1.31 (t, 3H); 1.55 (d, 3H); 1.72-1.87 (m, 2H); 2.17 (d, 2H); 2.98 (bt, 2H); 3.15-3.23 (m, 1H); 4.18 (q, 2H); 4.30 (bs, 2H); 4.56 (m, 1H); 5.01 (d, 1H, NH); 6.15 (s, 1H); 6.50 (d, 1H); 6.95 (dd, 2H); 7.22-7.46 (m, 5H); 7.45 (dd, 2H); 8.03 (d, 1H).

MS (m/z) CI: 531 (MH+, 100).

e) 4-(4-Fluorophenyl)-2-(piperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole



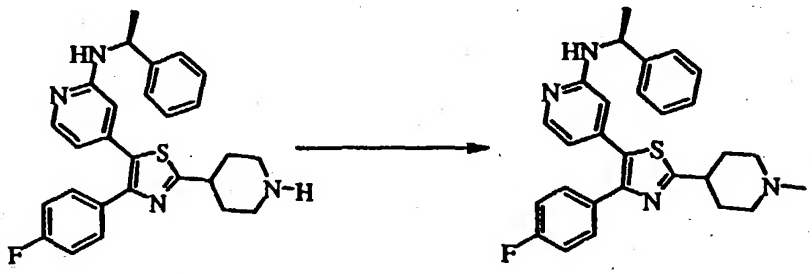
4-(4-Fluorophenyl)-2-(1-ethoxycarbonylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole (2g 3.7mmol) is dissolved in $CHCl_3$ (37ml) and treated with Me_3SiI (1.5ml 11.1mmol) at 60°C for 5h. A second portion of Me3SiI (0.75ml 5.55mmol) was added and stirring continued for another 3h at 60°C. The reaction mixture was combined with 6M HCl in propanol (15ml), homogenized by vigorous stirring, poured on 2N NaOH and extracted twice

with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether /MeOH / NH_3conc. 80/18/2) to yield the title compound (1.2g 71%) as a white foam.

1H-NMR (400MHz; $CDCl_3$): 1.53 (d, 3H); 1.77 (bs, 3H); 2.17 (bd, 2H); 2.78 (bt, 2H); 3.15 (bt, 1H); 3.35 (bd, 2H); 4.55 (m, 1H); 5.00 (d, 1H, NH); 6.17 (s, 1H); 6.50 (d, 1H); 6.97 (bt, 2H); 7.20-7.37 (m, 5H); 7.45 (bt, 2H); 8.02 (d, 1H).

MS (m/z) CI: 459 (MH+)

Example 4: 4-(4-Fluorophenyl)-2-(1-methylpiperidin-4-yl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole



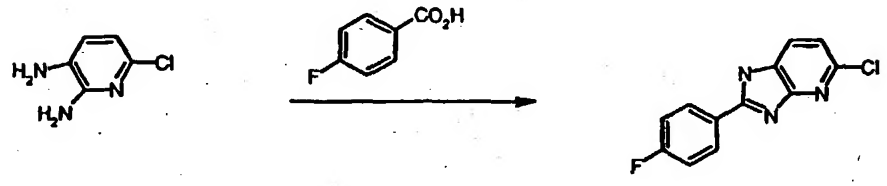
4-(4-Fluorophenyl)-2-(4-piperidinyl)-5-(2-(1-(S)-phenylethyl)amino-4-pyridinyl)thiazole (500mg 1.09mmol) is dissolved in MeOH (11ml) and treated with an aqueous 36%-solution of formaldehyde (0.17ml 2.18mmol) and $NaBH_4$ (83mg 2.18mmol), which is added as a solid in 3 portions. After 30min at room temperature the reaction mixture is poured on water and extracted three times with ethyl acetate. The combined organic phases are dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether /MeOH / NH_3conc. 95/4.5/0.5) to yield the title compound (550mg 86%) as pale yellow foam.

1H-NMR (400MHz; $CDCl_3$): 1.53 (d, 3H); 1.83-1.98 (m, 2H); 2.07-2.20 (m, 4H); 2.35 (s, 3H); 2.98 (bd, 3H); 4.55 (m, 1H); 4.98 (d, 1H, NH); 6.15 (s, 1H); 6.50 (d, 1H); 6.98 (t, 2H); 7.22-7.35 (m, 5H); 7.45 (dd, 2H); 8.02 (d, 1H).

MS (m/z) ESI: 473 (MH+)

Example 5: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo-[4,5-b]pyridine

a) 5-Chloro-2-(4-fluorophenyl)imidazo[4,5-b]pyridine

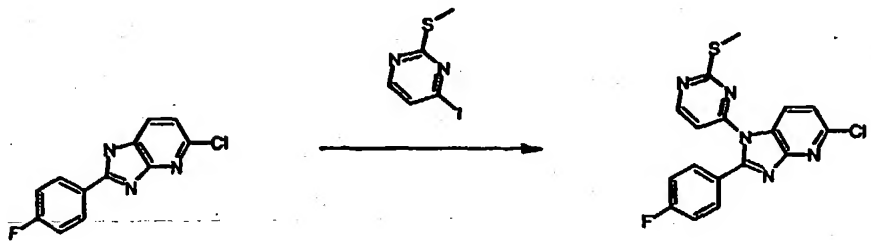


2,3-Diamino-6-chloropyridine (Davos-Bulk supplier, 2.25g 15.6mmol) and 4-fluorobenzoic acid (2.62g 18.7mmol) are treated with polyphosphoric acid (56.4g) at 150°C for 6h. The reaction mixture is poured on ice-water/NH_3conc. and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the crude product, which is purified by recrystallisation from ethyl acetate/tert.butyl methyl ether to yield the title compound (1.8g 44%) as grey crystals.

1H-NMR (400MHz; DMSO-d6): 7.32 (d, 1H); 7.47 (t, 2H); 8.08 (bd, 1H); 8.28 (q, 2H); 13.6 (s, 1H).

MS (m/z) ESI: 247 (MH+; 100).

b) 5-Chloro-2-(4-fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)imidazo[4,5-b]pyridine



$KN(TMS)_2$ (1.42g 7.16mmol) in toluene (7ml) is added at 0°C to a solution of 5-Chloro-2-(4-fluorophenyl)imidazo[4,5-b]pyridine (1.9g 6.66mmol) in DMF (25ml). After stirring 1h at room temperature, 2-methylthio-4-iodopyrimidine (1.8g 7.1mmol) in toluene (7ml) is added dropwise

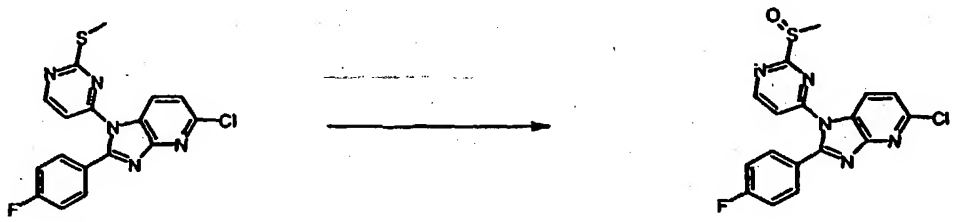
and heated for 20h at 120°C. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the crystalline crude product, which after recrystallisation from ethyl acetate yields the title compound as colorless crystals (1.76g 67%).

1H-NMR (400MHz; $CDCl_3$): 2.58 (s, 3H); 6.57 (d, 1H); 7.18 (t, 2H); 7.36 (d, 1H); 7.68 (q, 2H); 8.17 (d, 1H); 8.53 (d, 1H)

MS (m/z) ESI: 372 (MH+; 100); 352 (10); 336 (20).

The correct regiochemistry is demonstrated 2 steps later on the cyclopentylamine (d) analogue by ROESY.

c) 5-Chloro-2-(4-fluorophenyl)-1-(2-methylsulfinyl-4-pyrimidinyl)imidazo[4,5-b]pyridine

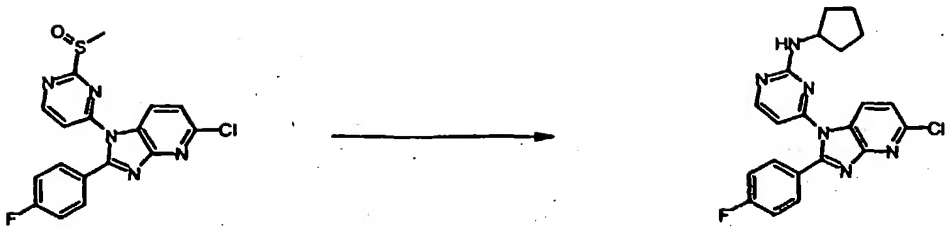


5-Chloro-2-(4-fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)imidazo[4,5-b]pyridine (372mg 1mmol) is dissolved in CH_2Cl_2/HOAc (7ml 5/2) and treated with mCPBA (270mg 70% 1.1mmol) at 0°C for 30min. The reaction mixture is poured on 2N Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (ethyl acetate) to yield the title compound (400mg 100%) as yellow foam.

1H-NMR (400MHz; $CDCl_3$): 3.08 (s, 3H); 6.92 (d, 1H); 7.25 (t, 2H); 7.42 (d, 1H); 7.68 (q, 2H); 8.55 (d, 1H); 8.78 (bs, 1H).

MS (m/z) ESI: 388 (MH+, 100); 352 (30).

d) 5-Chloro-2-(4-fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)imidazo[4,5-b]pyridine

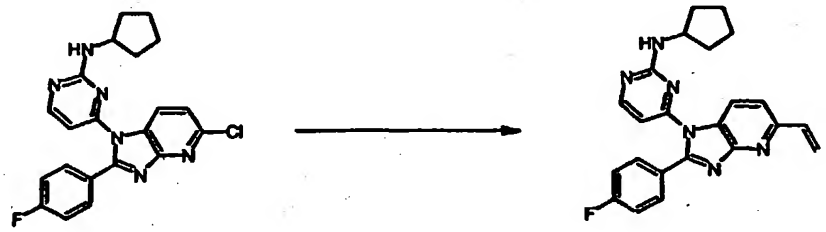


5-Chloro-2-(4-fluorophenyl)-1-(2-methylsulfinyl-4-pyrimidinyl)imidazo[4,5-b]pyridine (200mg 0.52mmol) and cyclopentylamine (1ml) are heated to 80°C for 1h, evaporated and purified by SiO_2 chromatography (acetone/cyclohexane 10/90 to 20/80) to yield the title compound as white crystals (50mg 24%).

1H-NMR (400MHz; $CDCl_3$): 1.43-1.86 (m, 6H); 1.95-2.20 (bs, 2H); 4.08-4.42 (bs, 1H); 5.30-5.52 (bs, 1H, NH); 6.20 (bs, 1H); 7.17 (t, 2H); 7.33 (d, 1H); 7.71 (q, 2H); 8.10 (d, 1H); 8.28 (d, 1H). The correct regiochemistry is demonstrated by ROESY.

MS (m/z) ESI: 409 (MH+, 100)

e) 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-vinylimidazo[4,5-b]pyridine

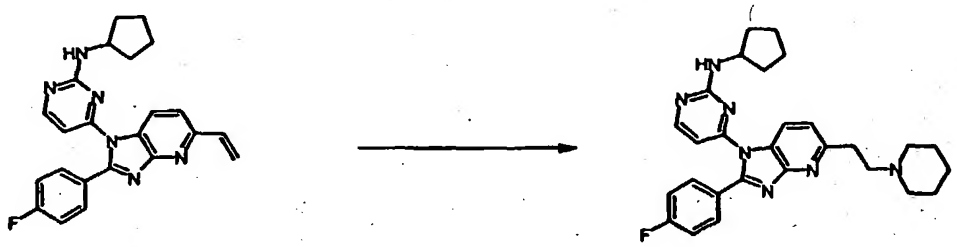


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-chloroimidazo[4,5-b]pyridine (50mg 0.12mmol), vinyltributylstannane (4.3ml 0.15mmol) and $PdCl_2(PPh_3)_2$ (8.6mg 0.01mmol) are dissolved in xylene (1ml) and heated to 160°C for 1h under argon. The reaction mixture is purified over SiO_2 (acetone/hexanes 15/85) to yield the title compound as colorless crystals (42mg 86%)

1H-NMR (400MHz; $CDCl_3$): 1.45-1.86 (m, 6H); 1.93-2.20 (bs, 2H); 4.06-4.48 (bs, 1H); 5.35 (bs, 1H, NH); 5.53 (d, 1H); 6.21 (bs, 1H); 6.44 (d, 1H); 6.95 (q, 1H); 7.18 (t, 2H); 7.48 (d, 1H); 7.73 (q, 2H); 8.08 (d, 1H); 8.30 (d, 1H).

MS (m/z) ESI: 399 (M-H).

f) 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidino-N-2-ethyl)imidazo-[4,5-b]pyridine

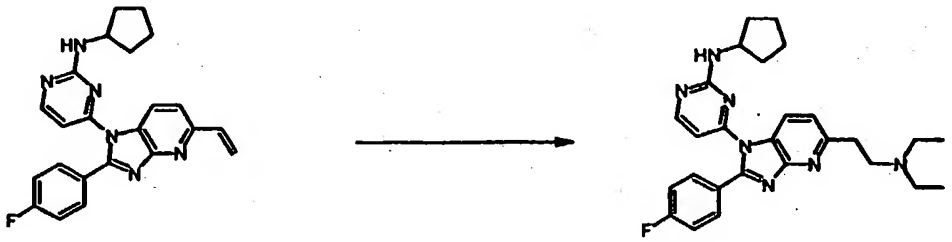


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-vinylimidazo[4,5-b]pyridine (50mg 0.13mmol) and piperidine (0.3ml 3mmol) are refluxed in HOAc (1ml) for 1.5h, poured on a saturated solution of Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered, evaporated to dryness and purified by SiO_2 chromatography (tert.butyl methyl ether/MeOH/NH_3conc. 85/15/1) to yield the title compound (60mg 98%) as yellow crystals.

1H-NMR (400MHz; DMSO, 120°C): 1.40-1.90 (m, 14H); 2.55 (bs, 2H); 2.75-2.91 (m, 4H); 3.08 (t, 2H); 4.03 (m, 1H); 6.43 (d, 1H); 6.97 (bs, 1H, NH); 7.28 (t, 3H); 7.69 (dd, 2H); 8.00 (d, 1H); 8.38 (d, 1H).

MS (m/z) ESI: 486 (MH+; 100)

Example 6: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(N,N-diethyl-amin -N-2-ethyl)imidazo[4,5-b]pyridine

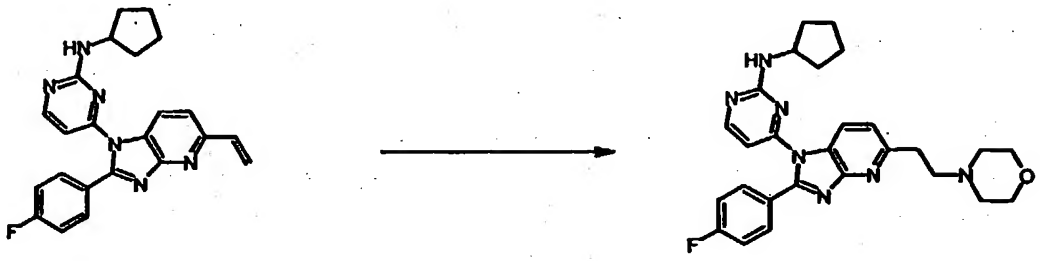


The crystalline title compound (48mg 50%) is prepared by analogy to the previous example.

1H-NMR (400MHz; $CDCl_3$): 1.12 (bt, 6H); 1.46-2.20 (m, 8H); 2.71 (bd, 4H); 2.97-3.20 (bd, 4H); 4.05-4.38 (bs, 1H); 5.35 (bs, 1H, NH); 6.18 (bs, 1H); 7.12 (t, 2H); 7.20 (d, 1H); 7.71 (dd, 2H); 8.03 (d, 1H); 8.29 (d, 1H).

MS (m/z) ESI: 474 (MH+, 100).

Example 7: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino-N-2-ethyl)imidazo[4,5-b]pyridine

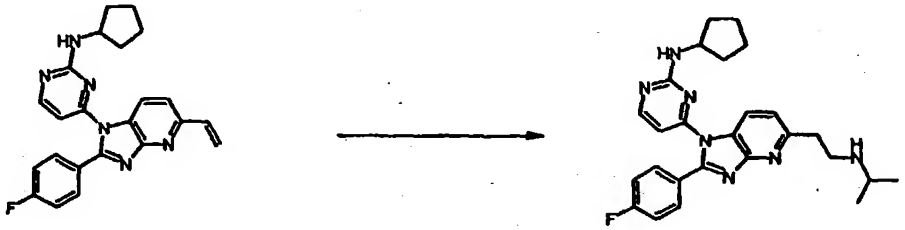


The crystalline title compound (78mg 66%) is prepared by analogy to the previous example.

1H-NMR (400MHz; $CDCl_3$): 1.45-1.85 (m, 6H); 1.93-2.13 (bs, 2H); 2.59 (bs, 4H); 2.95 (t, 2H); 3.18 (t, 2H); 3.78 (t, 4H); 4.03-4.41 (bs, 1H); 5.35 (bs, 1H, NH); 6.20 (bs, 1H); 7.15 (t, 2H); 7.20 (d, 1H); 7.72 (dd, 2H); 8.05 (d, 1H); 8.30 (d, 1H).

MS (m/z) ESI: 488 (MH+, 100);

Example 8: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(isopropylamino-N-2-ethyl)imidazo[4,5-b]pyridine

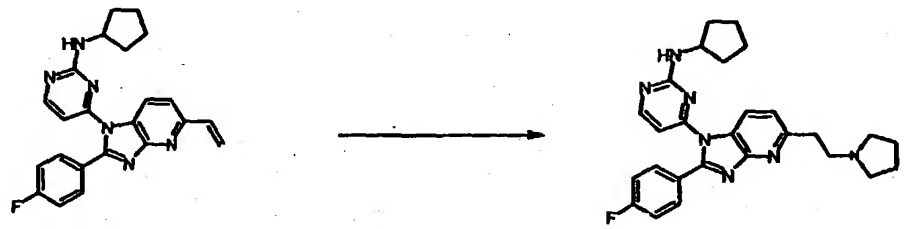


The crystalline title compound (30mg 33%) is prepared by analogy to the previous example.

1H-NMR (400MHz; $CDCl_3$): 1.15 (d, 6H); 1.45-2.15 (m, 8H); 2.95 (m, 1H); 3.21 (s, 4H); 4.08-4.35 (bs, 1H); 5.38 (bs, 1H, NH); 6.20 (bs, 1H); 7.16 (t, 2H); 7.22 (d, 1H); 7.73 (dd, 2H); 8.05 (d, 2H); 8.29 (d, 1H).

MS (m/z) ESI: 460 (MH+, 100).

Example 9: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyrrolidino-N-2-ethyl)imidazo[4,5-b]pyridine

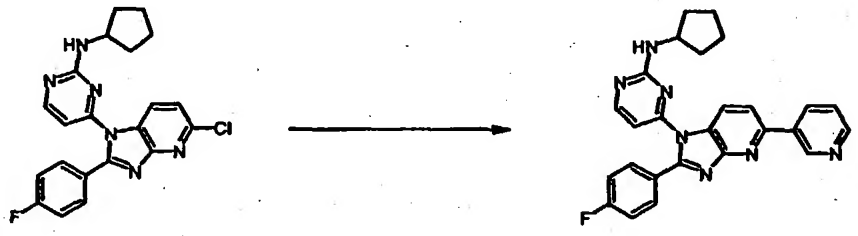


The crystalline title compound (34mg 36%) is prepared by analogy to the previous example.

1H-NMR (400MHz; $CDCl_3$): 1.45-2.18 (m, 12H); 2.65 (bs, 4H); 3.03 (m, 2H); 3.23 (m, 2H); 4.20 (bs, 1H); 5.35 (bs 1H, NH); 6.18 (bs, 1H); 7.14 (t, 2H); 7.22 (d, 1H); 7.74 (dd, 2H); 8.04 (d, 1H); 8.28 (d, 1H).

MS (m/z) ESI: 472 (MH+, 100).

Example 10: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-pyridyl)imidazo-[4,5-b]pyridine

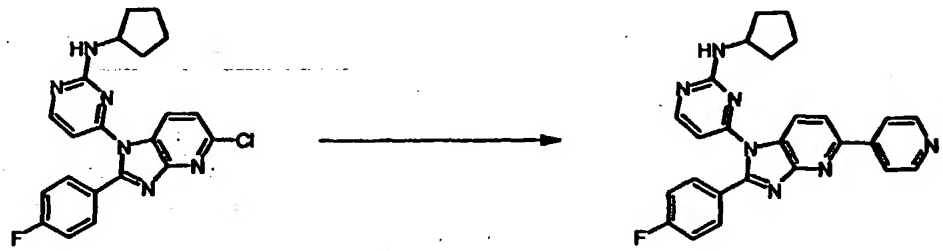


5-Chloro-2-(4-fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)imidazo[4,5-b]pyridine (2g 4.9mmol), 3-tributylstannylpyridine (3.6g 9.8mmol) and $PdCl_2(PPh_3)_2$ (340mg 0.48mmol) are heated in xylene (50ml) for 3h at 150°C under argon. The reaction mixture is filtered at 60°C and chromatographed over SiO_2 (acetone/hexanes 3/7 to 6/4) to yield pale yellow crystals (1.3g). Recrystallisation from THF/hexanes renders the title compound as colorless crystals (985mg 45%).

1H-NMR (400MHz; $CDCl_3$): 1.45-1.90 (m, 6H); 1.95-2.20 (bs, 2H); 4.08-4.45 (bs, 1H); 5.41 (bs, 1H, NH); 6.25 (bs, 1H); 7.18 (t, 2H); 7.48 (m, 1H); 7.78 (dd, 2H); 7.86 (d, 1H); 8.25 (d, 1H); 8.33 (d, 1H); 8.60 (d, 1H); 8.68 (d, 1H).9.38 (s, 1H).

MS (m/z) ESI: 450 (M-H).

Example 11: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridyl)imidazo[4,5-b]pyridine



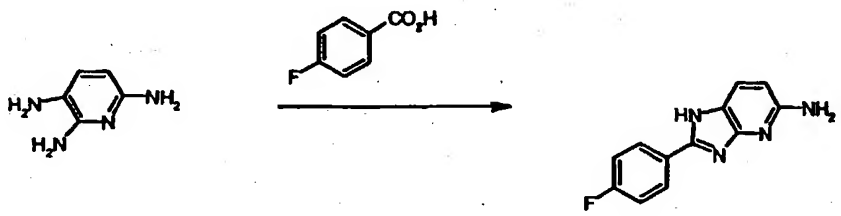
The white crystalline title compound (1.3g 70%) is obtained by analogy to the previous example with the exception that 4-trimethylstannylpyridine was used in the coupling reaction.

1H-NMR (400MHz; $CDCl_3$): 1.45-1.90 (m, 6H); 1.95-2.20 (bs, 2H); 4.08-4.45 (bs, 1H); 5.41 (bs, 1H, NH); 6.25 (bs, 1H); 7.18 (t, 2H); 7.78 (dd, 2H); 7.88 (d, 1H); 8.12 (d, 2H); 8.28 (d, 1H); 8.33 (d, 1H); 8.80 (d, 2H).

MS (m/z) ESI: 452.3 (MH+, 100).

Example 12: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine

a) 2-(4-Fluorophenyl)-5-aminoimidazo[4,5-b]pyridine

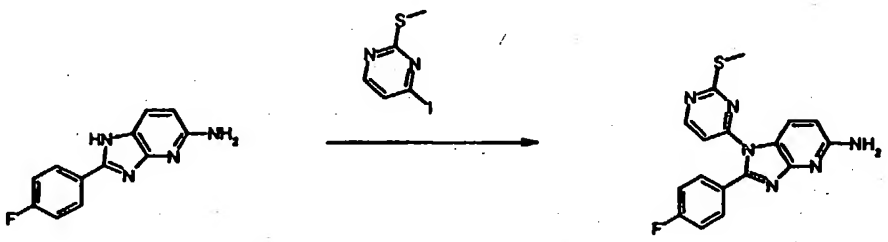


2,3,6-Triaminopyridine (Austin Products; 372mg 3mmol) and 4-fluorobenzoic acid (420mg 3mmol) are treated with polyphosphoric acid (30g) at 150°C for 1h. The reaction mixture is poured on ice-water/NH_3conc. and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the crude product, which is purified by SiO_2 chromatography (acetone/cyclohexane 20/80 to 50/80) and rendered the title compound as pale yellow crystals (200mg 29%)

1H-NMR (400MHz; DMSO): 5.92 (bs, 2H, NH2); 6.40 (d, 1H); 7.35 (t, 2H); 7.65 (d, 1H); 8.13 (dd, 2H); 12.80 (bs, 1H, NH).

MS (m/z) ESI: 229 (MH+, 100).

b) 2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine

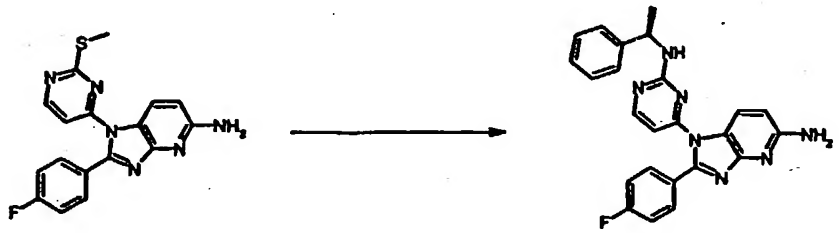


$KN(TMS)_2$ (688mg 3.65mmol) in toluene (3.5ml) is added at 0°C to a solution of 2-(4-fluorophenyl)-5-aminoimidazo[4,5-b]pyridine (684mg 3mmol) in DMF (10ml). After stirring 1h at room temperature, 2-methylthio-4-iodopyrimidine (832mg 3.3mmol) in toluene (3.3ml) is added dropwise and heated for 18h at 120°C. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the crude product, which is purified by SiO_2 chromatography (acetone/cyclohexane 20/80 to 60/40) and renders the title compound as a yellow foam (300mg 27%)

1H-NMR (400MHz; $CDCl_3$): 2.58 (s, 3H); 4.60 (bs, 2H, NH2); 6.55 (d, 1H); 6.59 (d, 1H); 7.16 (t, 2H); 7.63 (dd, 2H); 8.00 (d, 1H); 8.48 (d, 1H). The correct regiochemistry was demonstrated by ROESY.

MS (m/z) ESI: 353 (MH+, 100).

c) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine



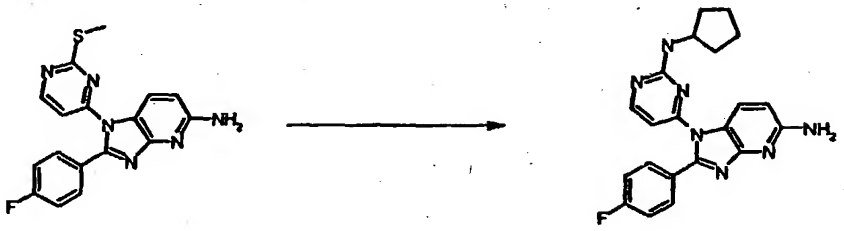
2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine (110mg, 0.31mmol) is dissolved in CH_2Cl_2/HOAc 1:1 (6.2ml), combined at 0°C with mCPBA (84mg 70%, 0.34mmol) and stirred for 30min. The reaction mixture is poured on 2N Na_2CO_3 and extracted

with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the crude sulfoxide (110mg). 50mg are dissolved in 1-(S)-phenylethylamine (0.5ml) and heated to 120°C for 1h. Purification over RP18 (CH_3CN/Water 70/30 to 10/90) yielded the title compound as light brown foam (30mg 52%)

1H-NMR (400MHz; $CDCl_3$): 1.60 (d, 3H); 4.50 (bs, 2H, NH2); 5.10 (bs, 1H); 5.78 (bs, 1H); 6.08 (d, 1H); 6.25 (bs, 1H); 7.11 (t, 2H); 7.37 (m, 1H); 7.41 (m, 5H); 7.63 (dd, 2H); 8.22 (d, 1H).

MS (m/z) EI: 425 (M+, 70); 410 (40).

Example 13: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-aminoimidazo[4,5-b]pyridine



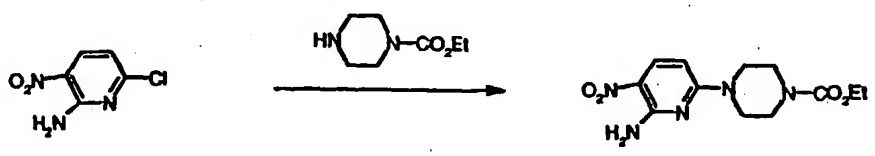
The title compound is prepared from the sulfoxide (60mg 0.16mmol) in the above procedure and cyclopentylamine (0.8ml) by heating to 120°C for 1h and purifying over RP18 (CH_3CN/Water 70/30 to 10/90). The title compound is obtained as a yellow powder (30mg 44%)

1H-NMR (400MHz; $CDCl_3$): 1.47-2.15 (m, 8H); 4.20 (bs, 1H); 4.55 (s, 2H; NH2); 5.34 (bs, 1H); 6.15 (s, 1H, NH); 6.54 (d, 1H); 7.12 (t, 2H); 7.68 (dd, 2H); 7.93 (d, 1H); 8.25 (d, 1H).

MS (m/z) EI: 389 (M+, 100).

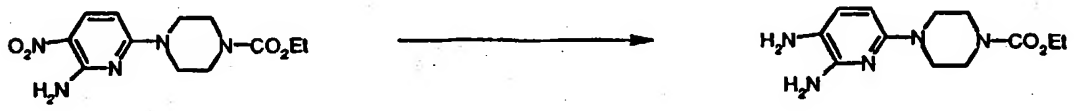
Example 14: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl) imidazo[4,5-b]pyridine

a) 5-Nitro-6-amino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine



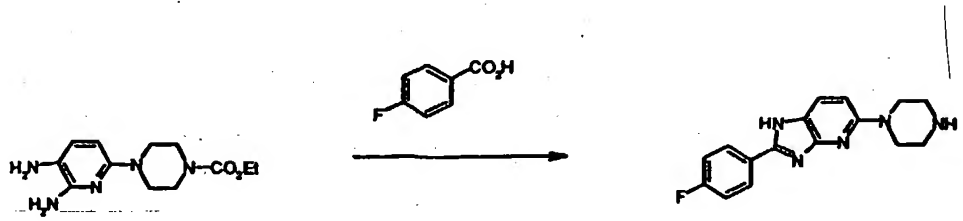
6-Amino-2-chloro-5-nitropyridine (Acros, 3.66g 21mmol) and 1-ethoxycarbonylpiperazine (6.36g 42mmol) in isopropanol (85ml) are refluxed for 3h. The reaction mixture with a yellow precipitate is poured on water/Na_2CO_3 and extracted twice with methylene chloride. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the title compound as yellow crystals, which are purified by recrystallisation from tert.-butyl methyl ether (5.5g 89%).
1H-NMR (400MHz; $CDCl_3$): 1.23 (t, 3H); 3.51 (m, 4H); 3.66 (m, 4H); 4.12 (q, 2H); 6.00 (d, 1H); 8.15 (d, 1H).
MS (m/z) EI: 295 (M+, 60); 193 (50); 167 (100).

b) 5,6-Diamino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine



5-Nitro-6-amino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine (4.5g 15.2mmol) in EtOH (200ml) is hydrogenated at 1 atm over 10% Pd/C (1.5g), filtered after hydrogen uptake was complete (2.5h), combined with 4-fluorobenzoic acid (2.13g 15.2mmol) in EtOH (50ml), evaporated to dryness and used without further purification in the following step.

c) 2-(4-Fluorophenyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine



The mixture of 5,6-Diamino-2-(4-ethoxycarbonyl-1-piperazinyl)pyridine from the previous hydrogenation (4.5g, 15.2mmol) and 4-fluorobenzoic acid (2.13g 15.2mmol) is treated with polyphosphoric acid (76g) at 150°C for 1h 15min. The reaction mixture is poured on ice-water/Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are

dried over Na_2SO_4, filtered and evaporated to dryness to yield the title compound as brownish crystals (1.6g, 35%).

1H-NMR (400MHz; DMSO): 2.73 (m, 4H); 3.43 (m, 4H); 6.78 (d, 1H); 7.35 (t, 2H); 7.80 (d, 1H); 8.18 (dd, 2H).

MS (m/z) CI:298 (MH+, 100); 278 (20).

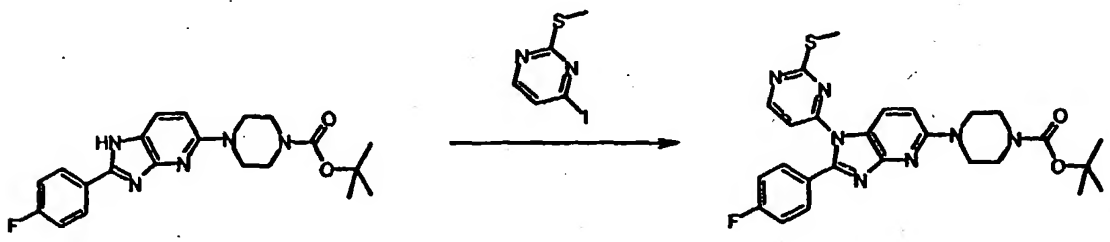
d) 2-(4-Fluorophenyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine

2-(4-Fluorophenyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine (1.57g, 5.3mmol) in THF (53ml) is treated with $(BOC)_2O$ (1.27g, 5.83mmol) for 30min. at room temperature, poured on water and extracted with ethyl acetate three times. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification over SiO_2 (acetone/hexanes 10/80 to 50/50) yields the title compound (1.6g, 74.5%) as brownish crystals.

1H-NMR (400MHz; $CDCl_3$): 1.52 (s, 9H); 3.52-3.73 (bs, 8H); 6.71 (d, 1H); 7.18 (t, 2H); 7.93 (bs, 1H); 8.07 (bt, 2H), 10.70 (bs, 1H, NH).

MS (m/z) EI: 397 (M+, 100); 341 (90); 241 (100).

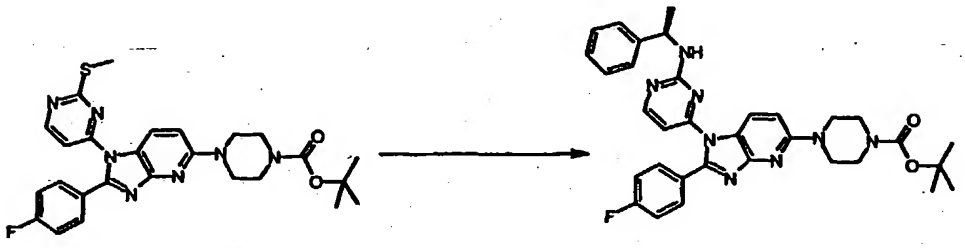
e) 2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl) imidazo[4,5-b]pyridine



$KN(TMS)_2$ (812mg, 3.85mmol) in toluene (3.85ml) is added at 0^0C to a solution of 2-(4-Fluorophenyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine (1.4g, 3.5mmol) in DMF (7ml). After stirring at room temperature for 30min., 4-iodo-2-methylthiopyrimidine

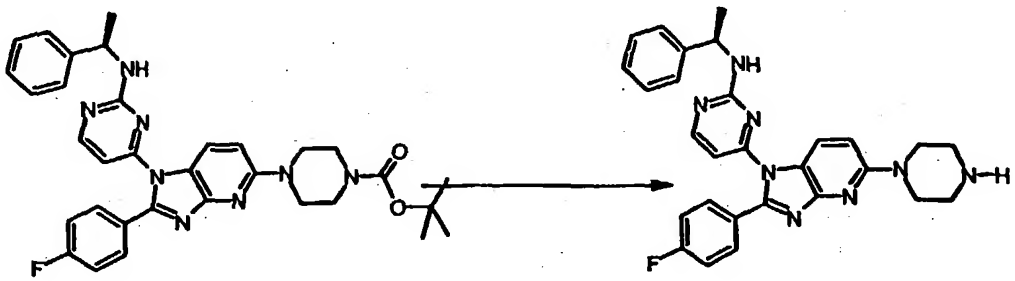
(970mg, 3.85mmol)in toluene (3.85ml) is added and the reaction stirred at room temperature for 1h. Toluene is evaporated, the reaction mixture heated to 120°C for 18h, poured on water and extracted with ethyl acetate (containing 5% EtOH) three times. The combined organic phases are washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification over SiO_2 (acetone/hexanes 20/80) renders the title compound (950mg, 52%) as colorless foam.
1H-NMR (400MHz; $CDCl_3$): 1.51 (s, 9H); 2.55 (s, 3H); 3.61 (m, 4H); 3.69 (m, 4H); 6.55 (d, 1H); 6.77 (d, 1H); 7.15 (t, 2H); 7.65 (dd, 2H); 8.06 (d, 1H); 8.47 (d, 1H). The correct regiochemistry was demonstrated by ROESY.
MS (m/z) ESI: 522 (MH+, 100).

f) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine



2-(4-Fluorophenyl)-1-(2-methylthio-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl) imidazo[4,5-b]pyridine (106mg, 0.2mmol) is dissolved in CH_2Cl_2/HOAc 1:1 (10ml), combined with mCPBA (113mg 70%, 0.24mmol) and stirred for 15min. The reaction mixture is poured on water and extracted with CH_2Cl_2 three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness to yield the crude sulfoxide (100mg), which is dissolved in 1-(S)-phenylethylamine (0.2ml) and heated to 120° C for 1h. Purification over SiO_2 (acetone/hexanes 1:1) yielded the title compound as colorless foam (45mg 35%)
1H-NMR (400MHz; $CDCl_3$): 1.51 (s, 9H); 1.62 (d, 3H); 3.58-3.67 (m, 8H); 5.10 (bs, 1H); 5.75 (bs, 1H); 6.08 (d, 1H); 6.45 (bs 1H, NH); 7.11 (t, 2H); 7.33-7.43 (m, 6H); 7.65 (dd, 2H); 8.22 (d, 1H).
MS (m/z) ESI: 595 (MH+, 100).

g) 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl) imidazo[4,5-b]pyridine



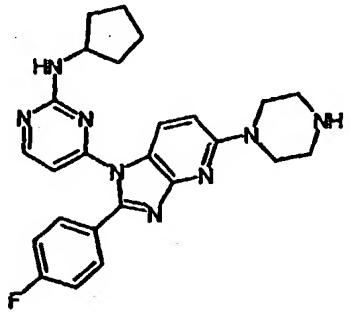
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-tert.butoxycarbonyl-1-piperazinyl)imidazo[4,5-b]pyridine (280mg, 0.67mmol) is dissolved in EtOH/HClconc 1/1 (9.4ml) and stirred at room temperature for 30min. The reaction mixture is poured on a saturated solution of Na_2CO_3 and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness. Purification over SiO_2 (tert.-butyl methyl ether/MeOH/NH_3conc 90/9/1) yields the title compound as a yellow foam (200mg, 86%)

1H-NMR (400MHz; $CDCl_3$): 1.61 (d, 3H); 1.89 (bs, 1H); 3.06 (bt, 4H); 3.62 (bt, 4H); 5.10 (bs, 1H); 5.75 (bs, 1H); 6.09 (d, 1H); 6.45 (bs, 1H); 7.05 (bs, 1H); 7.11 (t, 2H); 7.32-7.46 (m, 5H); 7.66 (dd, 2H); 8.21 (d, 1H).

MS (m/z) ESI: 495 (MH+, 100).

The compounds of Examples 15-17 are similarly prepared:

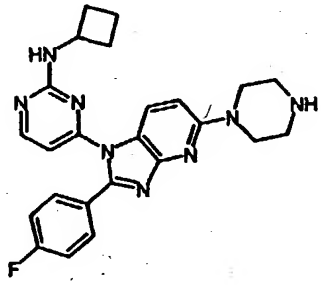
Example 15: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine:



1H-NMR (400MHz; DMSO-d6, 120°C): 1.43-1.58 (m, 4H); 1.65-1.75 (m, 2H); 1.80-1.90 (m, 2H); 3.10 (t, 4H); 3.73 (t, 4H); 4.00-4.08 (m, 1H); 6.38 (d, 1H); 6.90 (d, 1H); 6.95 (bd, 1H, NH); 7.26 (t, 2H); 7.68 (dd, 2H); 7.96 (d, 1H); 8.34 (d, 1H).

MS (m/z) ESI: 459.3 (MH+, 100).

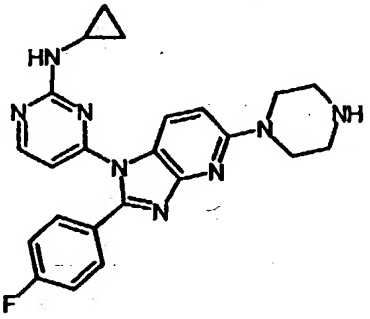
Example 16: 2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine:



1H-NMR (400MHz; CDCl3): 1.65-1.89 (m, 4H); 1.91-2.05 (m, 2H); 2.43 (bs, 1H); 3.06 (t, 4H); 3.67 (t, 4H); 4.40 (bs, 1H, NH); 5.50 (bd, 1H, NH); 6.17 (bd, 1H); 6.75 (d, 1H); 7.11 (t, 2H); 7.68 (dd, 2H); 7.97 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 445.3 (MH+, 100).

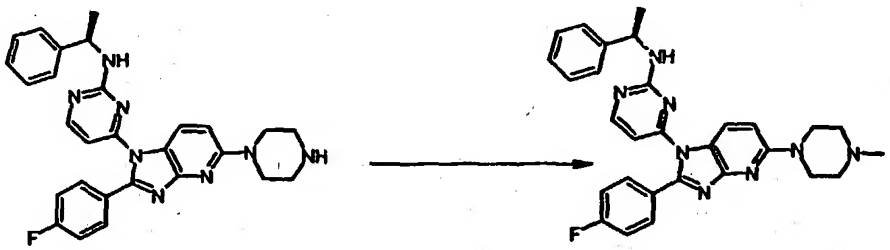
Example 17: 2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo[4,5-b]pyridine:



1H-NMR (400MHz; DMSO-d6): 0.47 (bs, 2H); 0.62 (bs, 2H); 2.33 (bs, 1H); 2.83 (bt, 4H); 3.47 (bt, 4H); 6.34 (bs, 1H); 6.92 (d, 1H, NH); 7.36 (t, 2H); 7.65 (dd, 2H); 7.85 (bd, 1H); 8.10 (bs, 1H); 8.36 (bd, 1H).

MS (m/z) ESI: 431.2 (MH+, 100).

Example 18: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl) imidazo[4,5-b]pyridine



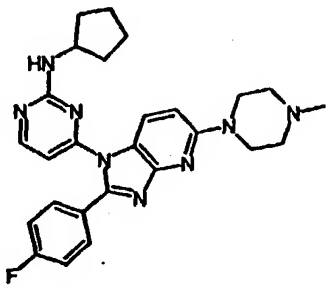
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl) imidazo[4,5-b]pyridine (50mg, 0.1mmol) is dissolved in MeOH (2.5ml). An aqueous 36%-solution of formaldehyde (15.8ml, 0.2mmol) is added and stirred for 30min. $NaBH_4$ (7.5mg, 0.2mmol) is added and stirring continued for 30min. The reaction mixture is poured on water and extracted with ethyl acetate three times. The combined organic phases are dried over Na_2SO_4, filtered and evaporated to dryness. Purification over SiO_2 (tert.-butyl methyl ether/MeOH/NH_3conc 90/9/1) yields the title compound as a yellow powder (35mg 68%)

1H-NMR (400MHz; $CDCl_3$): 1.61 (d, 3H); 2.40 (s, 3H); 2.60 (bt, 4H); 3.68 (bt, 4H); 5.12 (m., 1H); 5.76 (bs, 1H, NH); 6.08 (d, 1H); 6.48 (bs 1H); 7.10 (t, 2H); 7.35-7.46 (m, 6H); 7.66 (dd, 2H); 8.21 (d, 1H).

MS (m/z) ESI: 509 (MH+, 100).

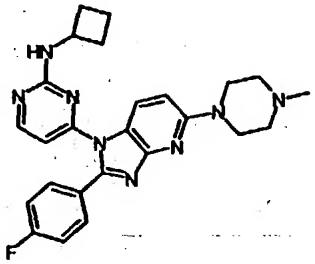
The compounds of Examples 19-21 are similarly prepared:

Example 19: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine:



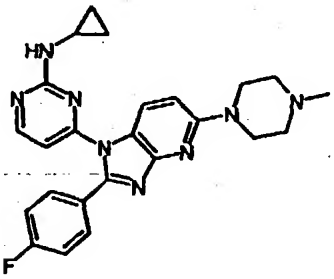
1H-NMR (400MHz; DMSO-d6): 1.45-1.58 (m, 2H); 1.61-1.83 (m, 4H); 1.97-2.13 (m, 2H); 2.38 (s, 3H); 2.59 (t, 4H); 3.71 (t, 4H); 4.10-4.31 (m, 1H); 5.33 (bd, 1H, NH); 6.16 (bs, 1H); 6.75 (d, 1H); 7.11 (t, 2H); 7.68 (dd, 2H); 7.97 (d, 1H); 8.23 (d, 1H).
MS (m/z) ESI: 473.3 (MH+, 100).

Example 20: 2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine:



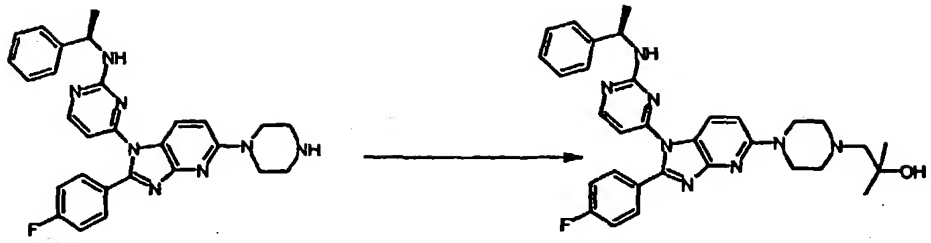
1H-NMR (400MHz; DMSO-d6): 1.45-2.12 (m, 6H); 2.20 (m, 1H); 2.25 (s, 3H); 2.45 (bt, 4H); 3.55 (bt, 4H); 6.95 (bs, 1H); 7.32 (t, 2H); 7.62 (bs, 2H); 7.93 (bd, 2H); 8.33 (bs, 1H).
MS (m/z) ESI: 459.3 (MH+, 100).

Example 21: 2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-methyl-1-piperazinyl)imidazo[4,5-b]pyridine:



1H-NMR (400MHz; CDCl3): 0.64 (m, 2H); 0.88 (m, 2H); 2.38 (s, 3H); 2.58 (t, 4H); 2.82 (bs, 1H); 3.72 (t, 4H); 5.58 (s, 1H, NH); 6.19 (d, 1H); 6.74 (d, 1H); 7.13 (t, 2H); 7.71 (dd, 2H); 8.12 (bs, 1H); 8.28 (bs , 1H).
MS (m/z) ESI: 445 (MH+, 100).

Example 22: 2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



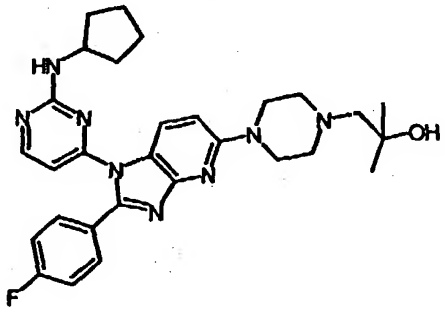
2-(4-Fluorophenyl)-1-(2-(1-(S)-phenylethyl)amino-4-pyrimidinyl)-5-(4-NH-1-piperazinyl)imidazo [4,5-b]pyridine (60mg, 0.12 mmol) and isobutyleneoxide (43.5ml 0.6mmol) in EtOH (6ml) are heated at 80°C for 3h. The reaction mixture is evaporated and purified by SiO_2 chromatography (tert.-butyl methyl ether/MeOH/NH_3conc. 97/2.7/0.3) to yield the title compound as a yellow foam (40mg 60%).

1H-NMR (400MHz; DMSO, 120°C): 1.18 (s, 6H); 1.48 (d, 3H); 2.43 (s, 2H); 2.72 (dd, 4H); 3.58 (dd, 4H); 5.10 (m, 1H); 6.32 (d, 1H); 6.73 (d, 1H); 7.21 (t, 2H); 7.28-7.38 (m, 5H); 7.43 (bd, 1H, NH); 7.62 (dd, 2H); 7.65 (d, 1H); 8.32 (d, 1H).

MS (m/z) ESI: 567 (MH+, 100).

The compounds of Examples 23-25 are similarly prepared:

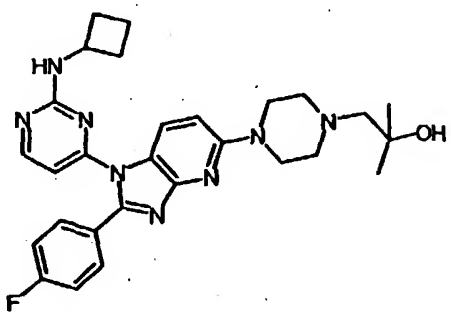
Example 23: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



1H-NMR (400MHz; DMSO): 1.24 (s, 6H); 1.52 (bs, 2H); 1.67 (bs, 2H); 1.79 (bs, 2H); 2.08 (bs, 2H); 2.42 (s, 2H); 2.82 (bt, 4H); 3.20 (bs, 1H, OH); 3.70 (bt, 4H); 4.22 (bs, 1H); 5.35 (bd, 1H, NH); 6.17 (bs, 1H); 6.74 (d, 1H); 7.12 (t, 2H); 7.70 (dd, 2H); 7.97 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 531.3 (MH+, 100).

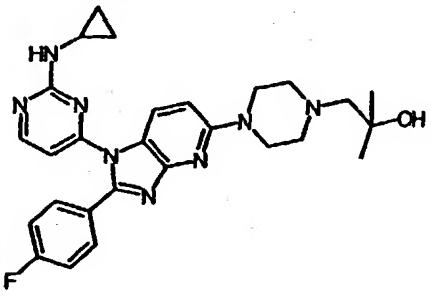
Example 24: 2-(4-Fluorophenyl)-1-(2-cyclobutylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



1H-NMR (400MHz; DMSO): 1.25 (s, 6H); 1.56-2.03 (m, 6H); 2.43 (s, 2H); 2.82 (t, 4H); 3.15 (bs, 1H, OH); 3.70 (t, 4H); 4.40 (bs, 1H, NH); 5.50 (bd, 1H, NH); 6.15 (bs, 1H); 6.74 (d, 1H); 7.12 (t, 2H); 7.69 (dd, 2H); 7.98 (d, 1H); 8.25 (d, 1H).

MS (m/z) ESI: 517.4 (MH+, 35).

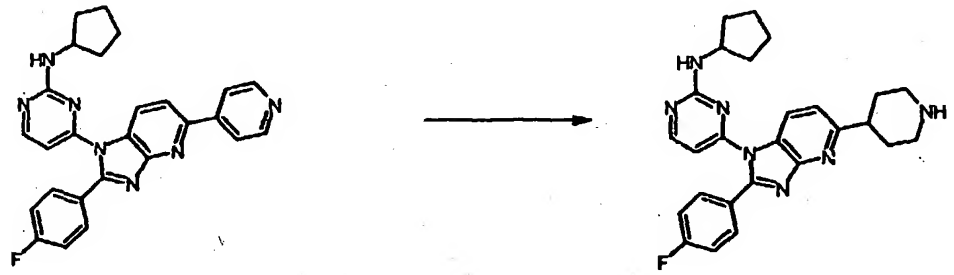
Example 25: 2-(4-Fluorophenyl)-1-(2-cyclopropylamino-4-pyrimidinyl)-5-(4-(2-hydroxy-2-methyl)propyl-1-piperazinyl)imidazo[4,5-b]pyridine



1H-NMR (400MHz; DMSO): 0.64 (m, 2H); 0.88 (m, 2H); 1.25 (s, 6H); 2.42 (s, 2H); 2.83 (m, 5H); 3.17 (s, 1H, OH); 3.70 (bt, 4H); 5.57 (s, 1H, NH); 6.20 (d, 1H); 6.73 (d, 1H); 7.13 (t, 2H); 7.71 (dd, 2H); 8.12 (bs, 1H); 8.29 (bs, 1H).

MS (m/z) ESI: 503.3 (MH+, 40).

Example 26: 2-(4-Fluorophenyl)-1-(2-cyclopentylamin -4-pyrimidinyl)-5-(4-piperidinyl) imidazo[4,5-b]pyridine

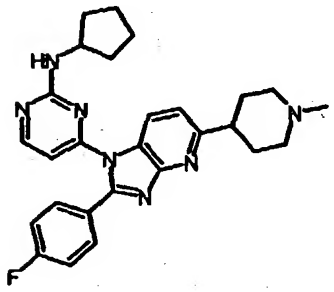


2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(4-pyridinyl)imidazo[4,5-b]pyridine (example 7; 100mg; 0.22mmol) is dissolved in HOAc (120ml) and hydrogenated over Pd/C (10%, 200mg) in a Parr apparatus for 48h at room temperature. The reaction mixture is filtered and evaporated to dryness delivering the title compound as yellow crystals, which are recrystallised from MeOH and gave the title compound as colorless crystals (70mg; 65%).

1H-NMR (400MHz; DMSO-d6, 120°C): 1.49 (m, 4H); 1.68 (m, 2H); 1.83 (m, 2H); 2.10 (m, 4H); 3.05 (dt, 4H); 3.18 (m, 1H); 3.48 (m, 4H); 4.03 (m, 1H); 6.45 (d, 1H); 7.05 (bd, 1H, NH); 7.30 (m, 2H); 7.70 (m, 2H); 8.08 (d, 1H); 8.40 (d, 1H).

MS (m/z) ESI: 458.3 (MH+; 100).

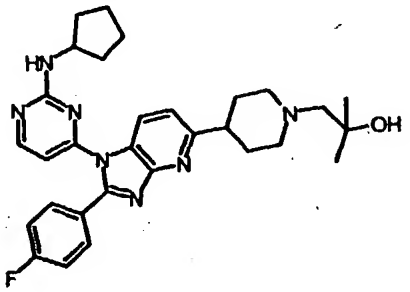
Example 27: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-methyl-4-piperidinyl)imidazo[4,5-b]pyridine



The title compound is prepared in analogy to Example 18.

MS (m/z) ESI: 472.4 (MH+, 100).

Example 28: 2-(4-Fluor phenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-(2-hydroxy-2-methyl)propyl-4-piperidinyl)imidazo[4,5-b]pyridine

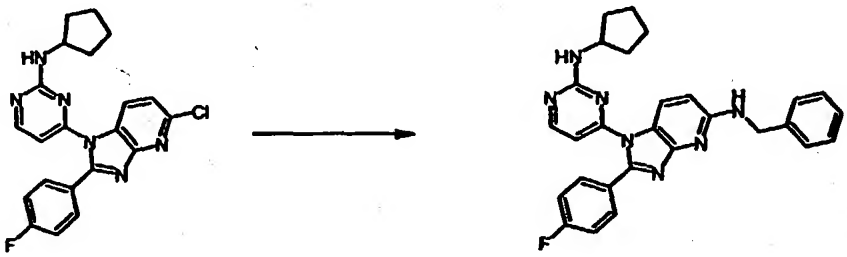


The title compound is prepared in analogy to Example 22.

1H-NMR (400MHz; DMSO-d6, 120°C): 1.21 (s, 6H); 1.43-1.83 (m, 8H); 1.95-2.18 (m, 5H); 2.41 (s, 2H); 2.56 (bt, 2H); 2.88 (bt, 1H); 3.08 (bd, 2H); 5.37 (bs, 1H, NH); 6.21 (bs, 1H); 7.13 (t, 2H); 7.21 (d, 1H); 7.72 (dd, 2H); 8.06 (d, 1H); 8.28 (d, 1H).

MS (m/z) ESI: 530 (MH+, 100)

Example 29: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(benzylamino) imidazo[4,5-b]pyridine



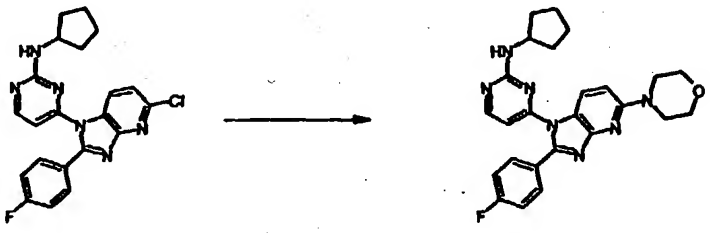
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(chloro)imidazo[4,5-b]pyridine (100mg; 0.25mmol), R-(+)-BINAP (10mg; 0.016mmol), $Pd_2(dba)_3$ (22mg; 0.024mmol) are suspended in xylene (16ml), benzylamine (0.53ml; 4.9mmol) is added, followed by NaOtBu (47mg; 0.49mmol) and heated to 160°C for 10 min. under argon. The reaction mixture is poured on water (100ml) containing HOAc (2ml) and extracted with TBME three times. The combined organic phases are washed with 2N Na_2CO_3, dried over Na_2SO_4 and evaporated to dryness. Purification via SiO_2 chromatography (TBME/hexane 6:4 to 10:0) and recrystallisation from TBME yields the title compound as colorless crystals (50mg: 50%).

1H-NMR (400MHz; $CDCl_3$): 1.45-1.85 (m, 6H); 1.95-2.13 (m, 2H); 4.25 (bs, 1H); 4.72 (d, 1H);

4.86 (bt, 1H, NH); 5.31 (bd, 1H, NH); 6.15 (, bs, 1H); 6.43 (d, 1H); 7.11 (t, 2H); 7.28 (m, 3H); 7.35 (t, 2H); 7.45 (d, 1H); 7.68 (dd, 2H); 7.89 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 480 (MH+, 100).

Example 30: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(morpholino) imidazo[4,5-b]pyridine



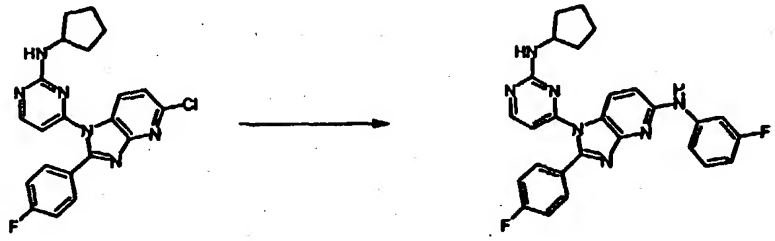
2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(chloro)imidazo[4,5-b]pyridine (100mg; 0.25mmol), R-(+)-BINAP (10mg; 0.016mmol), $Pd_2(dba)_3$ (22mg; 0.024mmol) are suspended in xylene (16ml), morpholine (0.43ml; 4.9mmol) is added, followed by NaOtBu (47mg; 0.49mmol) and heated to 160°C for 10 min. under argon. The reaction mixture is poured on water (100ml) containing HOAc (2ml) and extracted with TBME three times. The combined organic phases are washed with 2N Na_2CO_3, dried over Na_2SO_4 and evaporated to dryness. Purification via SiO_2 chromatography (TBME/hexane 7:3 to 10:0) and recrystallisation from TBME yields the title compound as colorless crystals (22mg: 19%).

1H-NMR (400MHz; $CDCl_3$): 1.47-1.84 (m, 6H); 1.97-2.17 (bs, 2H); 3.65 (m, 4H); 3.88 (m, 4H); 4.22 (bs, 1H); 5.33 (bs, 1H, NH); 6.16 (bs, 1H); 6.72 (d, 1H); 7.11 (t, 2H); 7.69 (dd, 2H); 8.00 (d, 1H); 8.25 (bd, 1H).

MS (m/z) ESI: 460 (MH+, 100).

Example 31: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(3-fluorophenyl amino)imidazo[4,5-b]pyridine

The title compound is prepared in analogy to Example 29

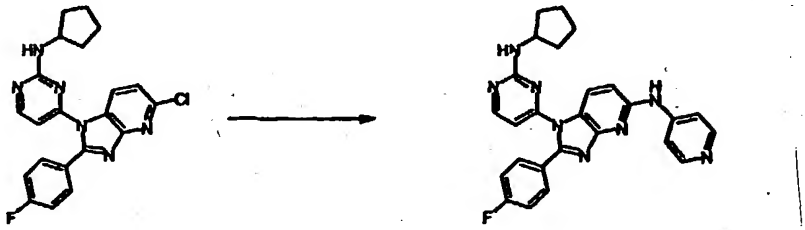


1H-NMR (400MHz, $CDCl_3$): 1.48-1.87 (m, 6H); 1.95-2.18 (m, 2H); 4.22 (s, 1H); 5.37 (bs, 1H, NH); 6.15 (bs, 1H); 6.72 (bs, 2H); 6.86 (d, 1H); 7.15 (t, 2H); 7.28 (m, 2H); 7.53 (d, 1H); 7.70 (dd, 2H); 8.03 (d, 1H); 8.27 (d, 1H).

MS (m/z) ESI: 484 (MH+, 100).

Example 32: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(pyridyl-4-amino)imidazo[4,5-b]pyridine

The title compound is prepared in analogy to Example 29.

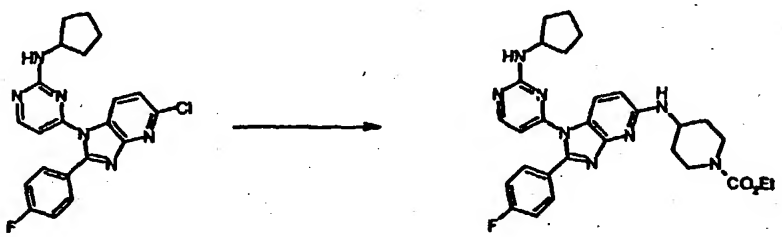


1H-NMR (400MHz, $CDCl_3$): 1.47-1.93 (m, 6H); 1.97-2.20 (m, 2H); 4.22 (m, 1H); 5.40 (d, 1H, NH); 6.17 (bs, 1H); 6.93 (d, 1H); 7.18 (m, 2H); 7.71 (m, 4H); 8.12 (d, 1H); 8.28 (d, 1H); 8.42 (d, 2H).

MS (m/z) ESI: 467 (MH+, 100).

Example 33: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonyl piperidine-4-amino)imidazo[4,5-b]pyridine

The title compound is prepared in analogy to Example 29



1H-NMR (400MHz, $CDCl_3$): 1.31 (t, 3H); 1.38-1.85 (m, 10H); 1.93-2.13 (bs, 1H); 2.21 (bd, 2H); 3.05 (bt, 2H); 4.03-4.39 (m, 4H); 5.33 (bs, 1H, NH); 6.15 (bs, 1H); 6.40 (d, 1H); 7.11 (t, 2H); 7.66 (dd, 2H); 7.88 (d, 1H); 8.23 (d, 1H).

MS (m/z) ESI: 545 (MH+, 100).

Example 34: 2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(piperidine-4-amino)imidazo[4,5-b]pyridine

2-(4-Fluorophenyl)-1-(2-cyclopentylamino-4-pyrimidinyl)-5-(1-ethoxycarbonylpiperidine-4-amino)imidazo[4,5-b]pyridine (58mg; 0.1mmol) is dissolved in $CHCl_3$ (2ml) and treated with trimethylsilyliodide (0.3ml; 2.2mmol) in a sealed vessel at 60°C for 5h. 6N HCl in isopropanol is added to the reaction mixture, which is then poured on 2N Na_2CO_3/ 2N NaOH and extracted with CH_2Cl_2 three times. The combined organic phases are dried over Na_2SO_4 and evaporated to dryness to yield the crude title compound, which is purified via recrystallisation from THF/TBME (44mg; 88%).

1H-NMR (400MHz, $CDCl_3$): 1.35-1.82 (m, 8H); 2.06 (bs, 2H); 2.22 (bd, 2H); 2.82 (bt, 2H);

3.15 (bd, 2H); 4.06-4.32 (m, 3H); 4.39 (d, 1H, NH); 5.32 (bd, 1H, NH); 6.14 (bs, 1H); 6.38 (d, 1H); 7.10 (t, 2H); 7.66 (dd, 2H); 7.87 (d, 1H); 8.23 (d, 1H).
MS (m/z) ESI: 473.1 (MH+, 100).

The Agents of the Invention, as defined above, e.g., of formula I, II and V particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

In particular Agents of the Invention possess p38 MAP kinase (Mitogen Activated Protein Kinase) inhibiting activity. Thus the Agents of the Invention act to inhibit production of inflammatory cytokines, such as TNF-α and IL-1, and also to potentially block the effects of these cytokines on their target cells. These and other pharmacological activities of the Agents of the Invention as may be demonstrated in standard test methods for example as described below:

p38 MAP kinase Assay

The substrate (GST-ATF-2; a fusion protein comprising amino acids 1-109 of ATF-2 and the GST protein obtained by expression in E. coli) is coated onto the wells of microtiter plates (50 µl/well; 1 µg/ml in PBS/0.02% Na azide) overnight at 4 °C. The following day, the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide and are blocked with PBS/2% BSA/0.02% Na Azide for 1 h at 37 °C. Plates are washed again 4 times with PBS/0.5% Tween 20/0.02% Na azide. The kinase cascade reaction is then started by adding the following reactants in 10 µl aliquots to a final reaction volume of 50 µl.

1. Agents of the Invention titrated from 10 to 0.001 µM in 10-fold dilutions or solvent (DMSO) or H_2O.
2. Kinase buffer (5x); pH 7.4; 125 mM Hepes (Stock at 1M; Gibco #15630-056), 125 mM β-glycerophosphate (Sigma #G-6251):125 mM $MgCl_2$ (Merck #5833); 0.5 mM Sodium orthovanadate (Sigma #5-6508), 10 mM DTT (Boehringer Mannheim #708992). The (5x) kinase buffer must be prepared fresh the day of the assay from 5x stock solutions kept at RT. DTT is kept at -20 °C and is added as the last reagent.

3. His-p38 MAP kinase (10 ng/well; Novartis - a fusion protein comprising full length murine p38 MAP kinase and a His tag, obtained by expression in E. coli)
4. cold ATP (final concentration 120 µM; Sigma #A-9187)
5. Water

After 1h at 37 °C the kinase reaction is terminated by washing the plates four times as previously described. Phosphorylated GST-ATF-2 is then detected by adding:

1. the PhosphoPlus ATF-2 (Thr71) Antibody (50 µl/well; 1/1000 final dilution in PBS/2% BSA/0.02% Na Azide; New England Biolabs #9221L) for 90 min at RT.
2. Biotin labelled goat-anti-rabbit IgG (50 µl/well; 1/3000 final dilution in PBS/2% BSA/0.02% Na Azide; Sigma #B-9642) for 90 min at RT.
3. Streptavidin-alkaline phosphatase (50 µl/well; 1/5000 dilution in PBS/2% BSA/0.02% Na Azide; Jackson Immunoresearch #016-050-084) for 30 min at RT.
4. Substrate (100 µl/well; Sigma 104 Phosphatase substrate tablets, 5 mg/tablet; #104-105; 1 mg/ml in substrate buffer, Diethanolamine (97 ml/l; Merck #803116) + $MgCl_2.6H_20$ (100 mg/l; Merck #5833) + Na Azide (0.2 g/l) + HCl 1M to pH 9.8) 30 min at RT.

After step 1,2 and 3 the microtiter plates are washed four times with PBS/0.5% Tween 20/0.02% Na azide. After step 4, the plates are read in a Bio-Rad microplate reader in a dual wavelength mode (measurement filter 405 nm and reference filter 490 nm). The bachground value (without ATP) is subtracted and IC_{50} values are calculated using the Origin computer program (4 parameter logistic function).

Agents of the Invention typically have IC_{50}s for p38 MAP kinase inhibition in the range from about 100 nM to about 5 nM or less when tested in the above assay.

Assay for Inhibition of TNF-α release from hPBMCs

Human peripheral blood mononuclear cells (hPBMCs) are prepared from the peripheral blood of healthy volunteers using ficoll-hypaque density separation according to the method of Hansell et al., J. Imm. Methods (1991) 145: 105. and used at a concentration of 10^5 cells/well in RPMI 1640 plus 10% FCS. Cells are incubated with serial dilutions of the test compounds for 30 minutes at 37°C prior to the addition of IFNg (100 U/ml) and LPS (5 mg/ ml) and subsequently further incubated for three hours. Incubation is terminated by centrifugation at 1400 RPM for 10 min. TNF-α in the supernatant

is measured using a commercial ELISA (Innotest hTNFa, available from Innogenetics N.V., Zwijnaarde, Belgium). Agents of the Invention are tested at concentrations of from 0 to 10 mM. Exemplified Agents of the Ivention typically suppress TNF release in this assay with an IC_{50} of from about ? nM to about ? nM or less when tested in this assay.

Assay for Inhibition of TNF-α Production in LPS stimulated mice

Injection of lipopolysaccharide (LPS) induces a rapid release of soluble tumour necrosis factor (TNF-α) into the periphery. This model is be used to analyse prospective blockers of TNF release in vivo.

LPS (20 mg/kg) is injected i.v. into OF1 mice (female, 8 week old). One (1) hour later blood is withdrawn from the animals and TNF levels are analysed in the plasma by an ELISA method using an antibody to TNF-α. Using 20 mg/kg of LPS levels of up to 15 ng of TNF-α / ml plasma are usually induced. Compounds to be evaluated are given either orally or s.c. 1 to 4 hours prior to the LPS injection. Inhibition of LPS-induced TNF-release is taken as the readout.

Agents of the Invention typically inhibit TNF production to the extent of up to about 50% or more in the above assay when administered at 10 mg/kg p.o.

As indicated in the above assays Agents of the Invention are potent inhibitors of TNF-α release. Accordingly, the Novel Compounds have pharmaceutical utility as follows:

Agents of the Invention are useful for the prophylaxis and treatment of diseases or pathological conditions mediated by cytokines such as TNFα and IL-1, e.g., inflammatory conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection, e.g. for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants and for the prevention of graft-versus-host disease, such as following bone marrow transplants.

Agents of the Invention are particularly useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with

an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific auto-immune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Agents of the Invention are also useful for the treatment, prevention, or amelioration of asthma, bronchitis, pneumoconiosis, pulmonary emphysema, and other obstructive or inflammatory diseases of the airways.

Agents of the Invention are useful for treating undesirable acute and hyperacute inflammatory reactions which are mediated by TNF, especially by TNFα, e.g., acute infections, for example septic shock (e.g., endotoxic shock and adult respiratory distress syndrome), meningitis, pneumonia; and severe burns; and for the treatment of cachexia or wasting syndrome associated with morbid TNF release, consequent to infection, cancer, or organ dysfunction, especially AIDS -related cachexia, e.g., associated with or consequential to HIV infection.

Agents of the Invention are also useful for the treatment of neurodegenerative diseases, such as Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligiodendrocyte loss in multiple sclerosis and inflammatory nervous system diseases, such as neuroinflammatory and stroke.

Agents of the Invention are particularly useful for treating diseases of bone metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides.

For the above indications the appropriate dosage will, of course, vary depending, for example, on the particular Agent of the Invention employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are obtained at daily dosages of from about 1 to about 10mg/kg/day p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 50 to about 750mg of an Agent of the Invention administered orally once or, more suitably, in divided dosages two to four times/day.

The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg of Agent of the Invention per unit dosage.

In accordance with the foregoing the present invention also provides in a further series of embodiments:

A. A method of inhibiting production of soluble TNF, especially TNFα, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.

B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune of inflammatory disease or condition.